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IT IS rare for the implicit harmony which exists between basic scientific research and clinical practice to be perceivable. Generally, professional rivalry and even suspicion is often openly displayed between clinicians and scientists, probably because the course from basic research to clinical application is sometimes so long and tortuous that it is difficult for each to see the contribution and value of the other. And yet, at the recent ECCO7 conference in November 1993, it was impossible not to perceive the successful and explicit collaboration between scientist and clinician, producing some of the most encouraging and important results for the understanding and treatment of cancer, some of which were presented at the conference.

This was exemplified by the research of Professor Bert Vogelstein (Baltimore, U.S.A.), which he described in his ESO Award Lecture on the genetics of colorectal cancer (CRC) and its clinical implications. The now famous genetic sequence from normal colon to metastatic cancer, involving the activation of one oncogene (k-*ras*) and the loss of three tumour suppressor genes (TSG) (APC, DCC and p53), was explained and interestingly, a new hypothetical "mutator gene" was discussed which may accelerate mutations of oncogenes and TSGs. The importance of this information to risk assessment, early diagnosis, treatment and prognosis was also discussed. The elucidation of the genetics of CRC was aided by the inherited genetic disorder adenomatous polyposis coli (APC), so it is gratifying that the treatment of this disease may be improved through the genetic knowledge gained. It is now possible to determine from peripheral blood cells whether young, asymptomatic relatives of an APC patient have the mutated APC gene and, therefore, predict the risk of the disease. Most would agree that prevention is the best form of treatment, and so by having an early diagnosis before symptoms appear, it will be possible to suppress the development of the polyps and thereby drastically improve the prognosis of such patients. Sulindac, an anti-inflammatory drug, has already been shown to regress polyps in APC patients, and could be used as a prevention measure. Currently, other drugs are being tested in animal models for this purpose, and Professor Vogelstein predicted that it should be possible in the near future to eradicate APC in the young.

Fig. 1. Professor Bert Vogelstein, Director of Molecular Genetics at the John Hopkins Oncology Centre, Baltimore, U.S.A. Winner of the 1993 ESO Pezcoller Award.

This was one of many examples presented at ECCO7 in which molecular techniques and discoveries played an invaluable role in understanding neoplasia. However, Professor Claude Hélène (Paris, France) convincingly put forward potential therapies which will be molecular techniques, thus controlling aberrant gene expression with specially synthesised oligonucleotides. He suggested four possible strategies: antisense, in which the target would be mRNA so as to ultimately affect DNA double helix formation; antigene, in which DNA would be targetted, blocking transcription of the gene; sense, in which protein would be the target, affecting gene expression by blocking transcription factors; and ribozyme, where again mRNA would be the target, resulting in its catalytic cleavage. The description of these strategies and the practicalities seemed so futuristic to be almost in the realms of science fiction, and yet clinical trials are already underway, testing antisense oligonucleotides for the treatment of chronic myelocytic leukaemia, acute myeloblastic leukaemia and HIV and human papilloma virus (cervical cancer) infections. The use of oligonucleotides as pharmaceuticals is feasible, with large scale synthesis possible, toxicity and degradation products apparently minimal, and clearance/pharmacokinetics showing uniform distribution in all tissues except the brain. Thus, "gene pharmacology" may become a reality before very long.

The current excitement generated by advances in molecular oncology has inevitably led to an impression that, in the future, it will be solely responsible for any eradication of cancer. This is unlikely to be true. The importance of more traditional research cannot be denied, and indeed examples were presented at ECCO7 where vital developments and discoveries have been made simply through intelligent deduction or fortuitous observation. The discovery of sulindac for the treatment of APC, as mentioned by Professor Vogelstein, is such a case. Its effectiveness in polyp regression was first noted by a local general practitioner in the U.S.A., Dr Bill Wardell, who had prescribed sulindac for other reasons to one of his patients with familial polyposis. This observation was published in 1982, 8 years before the genetic model for CRC was published.

Professor Harald Zur Hausen (Heidleberg, Germany) highlighted the fact that a substantial proportion of neoplasia, approximately 15% of all worldwide cancer, 20% in females and 10% in males, is either a direct or indirect result of viral infection, a factor which has been largely ignored by most researchers. He suggested that this was probably because it does not fit with the

oncogene/TSG theories! Viral DNA in infected cells can be repressed by two main pathways: an intracellular pathway, which prevents the immortalisation of the cell and an intercellular pathway, which prevents the spread and rapid increase in number of such "immortal" cells. It is environmental factors, such as smoking, chronic infections, hormones, immunodeficiency and the viruses themselves, which are known to break down these pathways. Thus, this is an area in need of attention.

Innovation in the development of new therapies was demonstrated by Professor Lejeune (Lausanne, Switzerland), recipient of the 1993 ESSO Award, with his new treatment of sarcoma or malignant melanoma of the limb. The cytokine, α-tumour necrosis factor (TNF), although tumoricidal, is not often used clinically because of its high, generalised toxicity. However, Professor Leujeune and his collaborators have devised a system whereby a limb can be isolated by attaching it to a heart and lung machine, and then treated with 10 times the maximum tolerated dose of α-TNF, in addition to mephalen and low dose interferon. This "isolation perfusion" technique has produced complete remission in 91% of patients compared with a 50% response rate with mephalen alone, and the duration of the response is approximately 3.6 years so far. Randomised trials are now underway. This new development is a regional therapy and, therefore, does not affect survival, but it does prevent limb amputation, which is a drastic improvement for the patients.

The clinical use of cytokines and growth factors, specifically in relation to haematopoiesis, was the subject of a lecture by Professor Leo Sachs (Rehovot, Israel). He elegantly described their effects, emphasising the interactions which occur between all these factors as they work directly or indirectly on each other to produce the required cell population. The balance between the different factors determines cellular outcome, i.e. maintenance of viability, multiplication, differentiation or death. He stressed that this must be considered when using the factors clinically, since the timing of doses could have an enormous impact on the effectiveness of the therapy. For example, if CSFs are given with chemotherapy at the wrong time, then there may be little or no effect on the cancer because the CSFs, which are viability factors, prevent apoptosis and so the cancerous cells continue to grow, i.e. the viability factors are preventing cellular death. Thus, the aim is to selectively remove the viability factors from malignant cells but not from normal cells, so that the former but not the latter will undergo apoptosis. It was encouraging to hear Professor Sachs underline the fact that cancer cells are not immortal, but still possess suppressed mechanisms for differentiation and apoptosis, and that it is the triggering of these in malignant cells which is the key to cancer therapy.

It has been said that any scientific conference which takes more than 2 years to organise can have very little to offer that is novel or fresh. However, at ECCO7 much was presented which was innovative, both in basic research and in clinical practice, and of value to many, as indicated by the enthusiastic attendances at most sessions. It was encouraging to see so many delegates from outside western Europe, particularly from countries in which dissemination of scientific information is slow at best, and perhaps even non-existent. ECCO7 was an excellent opportunity for the experienced to teach, and the inexperienced to learn, borne out by the almost capacity attendances at the early morning teaching lectures. For most, the meeting in Jerusalem was worthwhile.

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How Long Have I Got Doctor?

E.J. Maher

IT IS a brave physician who gives an unambiguous answer to the question, "How long have I got?" Predictions of survival for patients with advanced and metastatic cancer are notoriously inaccurate [1–5].

Recent papers [5–7] suggest that with increasing experience clinicians can place patients with advanced cancer into good and bad prognostic groups, but absolute predictions tend to be overoptimistic [8]. This has important resource implications. It has been estimated that $19 million per year are spent on palliative radiation therapy alone in the U.S.A. on patients with a medical survival of < 1 year [9]. Surveys of practice, relating predicted survival of specific cases and therapy proposed, show that differences of a few months in predicted survival can be related to 2- or 3-fold differences in the number of radiation treatments offered, or whether chemotherapy is offered at all [1, 8, 10]. On the other hand, poor prognosis does not seem to be associated with less intervention, or less anti-cancer therapy in the terminal phase of illness [5].

A wide range of factors have been suggested as of predictive value in studies of patients with advanced and or 'terminal' disease [2–4, 11–16], but the only durable powerful predictive factor remains performance status [5, 11, 16]. Intriguingly, quality of life indices have been found by some workers to be important prognostic indicators [15–17] but this has not been found by all workers [18–20].

In the current economic climate, there are likely to be increasing pressures to characterise 'isoprognostic' groups of patients, to allow appropriate stratification of clinical trials, interpret audit of survival after therapy in different centres as part of comparative audit, and to assist in difficult decisions

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