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Editorial

40 Years on – dreams, realities and appropriate optimism

The *European Journal of Cancer (EJC)* was launched in 1964 and is now celebrating its 40th anniversary. The first issues contained articles in English, French and German covering aspects of epidemiology, basic science, drug development and clinical research. Whilst now only published in English, the *EJC* remains multidisciplinary and truly European in its scope and appeal. To celebrate this anniversary, we have chosen seven of the original papers and invited experts in the relevant fields to write updates that give perspective on the development of these areas over the intervening years. They have not been asked to "review" 40 years of progress (or otherwise), but their commentaries are highly illuminating – and give food for thought regarding the concept of "real progress". Over 100 years ago George Bernard Shaw wrote

> "The reasonable man adapts himself to the world: the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man!" (from "Reason").

Does this remind you of any colleagues? At the time of the first issue I was an undergraduate at Cambridge University and understandably knew virtually nothing of what we now call cancer medicine. However, reading these original papers I find that I was not entirely alone! How little was known then and how much we have learnt over 40 years! Especially about cancer therapeutics. Training in medical oncology in the 1970s, I was one of the junior members of Gordon Hamilton–Fairley's team at St. Bartholomew's Hospital, London that introduced mechlorethamine vincristine, procarbazine, prednisone (MOPP) like chemotherapy for Hodgkin's disease in the United Kingdom. The remarkable remissions that were achieved launched the concept of combination chemotherapy, and the continuing struggle to achieve selectivity over tumour versus host tissue. The 1970s also saw the arrival of doxorubicin, the Cyclophosphamide, methotrexate, 5-fluorouracial (CMF) combination for breast cancer and cisplatinum with its dramatic contribution to the treatment of testis and ovarian cancer.

The 1980s were remarkable for developments in supportive care. Many believe that the development of 5HT3 anti-emetics was the most significant development in cancer therapeutics in recent memory. Developments in understanding stem cell biology led to the development of haematopoietic growth factors for bone marrow rescue or prevention. Subsequent over-enthusiasm for "high-dose" therapies have proven much less useful, but improvements in all aspects of supportive care have greatly enhanced the range of options available to patients – young and old.

The last 10–15 years has seen an explosion of scientific knowledge relevant to our understanding of cancer and its management. Molecular biology, and especially molecular genetics, has transformed our understanding of the subtle differences in growth regulation and metabolism between malignant and normal cells, and whilst the Human Genome Project has certainly created more questions than answers, we are already unravelling cancer phenotypes at the molecular level and identifying "targets" that are proving realistic for therapeutic interventions – the concept of which was only a dream 40 years ago. The papers in this *EJC* Special Issue reflect some of the highlights of this remarkable (and very short) 40 years of cancer research.

Procarbazine (Natulan) [PCB] one of the four drugs in the MOPP regime was the subject of Kenis's paper in volume 1 and its fate is reviewed here by Massoud and colleagues. Originally synthesised as part of a programme searching for monoamine oxidase inhibitors, this methylhydrazine derivative was found to have anti-tumour activity in models of transplantable tumours in mice and rats. PCB's contribution to the cure of Hodgkin's disease was unquestionable, but severe toxicities – in particular the development of secondary acute leukaemia led to its replacement by doxorubicin – based combinations – especially doxorubicin, bleomycin, vincristine, dacarbazine (ABVD). Studies of the mechanism of action of PCB demonstrated the generation of reactive oxygen species (ROS), such as hydrogen peroxide, and in volume 2 Berneis and colleagues ascribed this mechanism to the potentiation of ionising radiation by PCB. In this issue, Renschler reviews the emerging role of ROS in radiation potentiation, starting from PCB, through the era of nitroimidazoles such as misonidazole to the current interest in agents such as buthiomine sulfoximine and motexafin gadolinium.

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Over the past 40 years, drug development, including screening and mechanistic studies, has depended to a great extent on the available technology. Of particular relevance to this has been our ability to distinguish normal from tumour cell growth, and to model human cancers in the laboratory. In volume 1, Sandritter describes the technique of cytophotometry to demonstrate that human tumour cell nuclei exhibit an atypical distribution of DNA content. In this issue, Ansell reflects on the "essentially similar" cytophotometric methods of estimating DNA content in use today, with the advantage of digital imaging and software to allow more rapid sampling of many more nuclei. Ansell reviews the development of flow cytometry and karyotypic analysis that facilitated the description of the chromosomal basis for aneuploidy.

In volume 1, Hughes's paper on "The role of chromosomes in the characterisation of human neoplasms" reminds us that 40 years ago it was appreciated that chromosome hetroploidy of cell populations was associated with malignancy – of potential use in diagnosis. The value of studying premalignant and early neoplasms was predicted, as was the study of familial cancers, particularly hypothesising that structurally unbalanced karyotypes may predispose to cancer. In this issue, Young points out that several of the key events in the history of molecular cytogenetics were already identified and the subject of research at the time of Harris's publication. These included the Philadelphia translocation and the observation of a deleted chromosome in retinoblastoma and double-minute chromosomes in neuroblastoma. There have of course been highly significant technical advances over the past 40 years and Young reviews the way in which modern techniques such as fluorescence *in situ* hybridisation, comparative genomic hybridisation (CGH) and the recently developed array CGH technique are now incorporated into most diagnostic laboratories, to compliment chromosomal analysis and provide gene expression profiling that is set to revolutionise patient management. The first classifications of cancer based on modern techniques for gene expression have been applied to haematological malignancies, but are now being explored for the refinement of diagnosis in solid tumours.

How have tumour models served us in understanding cancer development and control? In this issue, Hirst and Balmain review 40 years of cancer modelling in the mouse, with some appropriate health warnings for future research in this area! Reflecting that in volume 2, Humphries and his colleagues started their paper with the statement "The transplantable tumour has been the principal tool in the experimental evaluation of anticancer agents", Hirst comments that "Sadly this statement is just as relevant today as it was 40 years ago!". Outlining progress in the manipulation of the mouse germ-line to study oncogenesis, developments in molecular imaging of cancer in the mouse, the study of environmental stress and mouse models of genetic susceptibility to cancer, Hirst and Balmain challenge the pharmaceutical industry and academia to reappraise the contribution of appropriate mouse models in the assessment of new "designer" drugs – particularly making use of primary as opposed to transplantable tumours.

Few areas of cancer research attract greater current interest than the biology and potential therapeutic use of stem cells. The haematopoietic system was the first to be studied and in this issue De Vries and her colleagues write of, "The happy destiny of frozen haematopoietic stem cells". Forty years ago Van Putten's paper in volume 1 described different storage techniques for mouse and monkey marrow, which led in due course to the ability to store autologous human bone marrow for use in "rescue" and eventually allogeneic transplantation. De Vries reviews current techniques for sourcing stem cells, indications for haematopoietic stem cell transplantation and the emerging concept of "developmental plasticity", where haematopoietic stem cells may be encouraged to "live happily" in various tissues of the body contributing to the repair of liver, cardiac or brain tissue, for example.

Much of the above relates to the management of cancer as an established disease, but ultimately prevention is an even greater goal. Prevention requires an understanding of causality and in volume one Harris addressed the relationship of viruses to the development of tumours. Forty years ago whilst acknowledging the established link between viruses and animal cancer (spontaneous and inducible), there was no proof of a viral link to human cancer. In this issue, Talbot and Crawford update the story not only attributing one fifth of all human cancers to a viral aetiology, but supporting the claim that most of these (gastric, hepatic, cervical) would be preventable with appropriate eradication of the relevant viral infections. In Harris's day, the isolation of viruses from tumours was technically difficult, but this has been revolutionised with the advent of modern techniques in molecular biology, complemented by polymerase chain reaction screening techniques that greatly enhance the speed of epidemiological studies.

> "The thing that hath been, it is that which shall be; and that which is done is that which shall be done; and there is no new thing under the sun" (Ecclesiastes).

Reviewing the papers that our Founding Editor Henri Tagnon selected 40 years ago for the 1st volume of *EJC*, and reading the excellent updates that we are publishing today, it is tempting to be cynical and ask

whether there is truly "anything new under the sun". I prefer the opposite optimistic attitude that congratulates our colleagues of the 1960s for the appropriateness of their scientific research, and the foresights with which they helped to shape cancer research over the ensuing four decades. If any of today's medical students happen to read this 40 years hence, I hope that our current endeavours will stand the test of time so successfully!

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