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New approaches needed for advanced lung cancer

Chemotherapy offers only marginal benefits for patients with advanced lung cancer and new combinations are unlikely to make substantial improvements in survival, a commentator writes (*N Engl J Med* 2002, **346**, 126–128). "Twenty years of clinical trials ... have yielded an improvement in survival of only two months," according to Dr Desmond Carney (Mater Misericordiae Hospital, Dublin, Ireland). "It is clear that new approaches are needed."

He was responding to two studies on chemotherapy regimes. The first, from the Japan Clinical Oncology Group (*N Engl J Med* 2002, **346**, 85–91), included patients with extensive small-cell lung cancer, who were given cisplatin plus either irinotecan or etoposide. They found that the combination of irinotecan and cisplatin is "an attractive option". At 2 years, 19.5% of patients on this regime survived, compared with 5.2% in the etoposide plus cisplatin group. Dr Carney said these results are "impressive" but that "Confirmatory trials are required before the new combination becomes the standard of therapy for this disease."

The second study (*N Engl J Med* 2002, **346**, 92–98) compared four chemotherapy regimes for lung cancer: cisplatin and paclitaxel; cisplatin and gemcitabine; cisplatin and docetaxel; or carboplatin and paclitaxel. They analysed data from 1155 randomised patients, followed for 2 years, and found that none of the regimes offered a significant advantage over the others. Carboplatin and paclitaxel had a lower rate of toxic effects and this regime has been chosen by the authors, the US-based Eastern Cooperative Oncology Group, as its reference regimen for future studies.

Dr Carney says that use of chemotherapy for advanced small cell lung cancer is nonspecific, nonselective and toxic. "New combinations of chemotherapy are not likely to make substantial improvements in survival."

Novel biological agents such as the tyrosine kinase inhibitors currently entering phase I and phase II trials offer more hope. He concludes, "Prevention, early detection, and the use of specific biologic targets offer optimism and hope that mortality from this disease may be reduced."

New marker for vulvar cancer

Measurement of the CD44 isoform CD44v3 in patients with vulvar cancer may give valuable prognostic information, researchers say. A joint Austrian/Australian/Dutch study found that over-expression of CD44v3 was associated with reduced disease-free and overall survival (*Cancer* 2002, **94**, 125–130). It was independent of tumour stage and lymph node status.

Researchers examined tissue samples from 99 patients and performed multivariate analysis. Their results confirm previous results from a univariate analysis, but the say, "Clinical use of CD44v6 as an additional stratification marker in prospective studies involving patients with vulvar cancinoma remains to be determined."

Radiotherapy in rectal cancer: an answer

Adjuvant radiotherapy is of benefit for patients with rectal cancer, a meta-analysis concludes (*Lancet* 2001, **358**, 1291–1304). It found only a marginal benefit in 5-year survival among patients who received either pre- or postoperative radiotherapy, but a significant reduction in the risk of local recurrence.

The systematic overview, conducted by the international Colorectal Cancer Collaborative Group, pooled data from 22 randomised trials. Data on more than 8000 individual patients were analysed.

Yearly risk of local recurrence was 46% lower in those who had preoperative radiotherapy than in those who had surgery alone. It was 37% lower in those who had postoperative treatment than among the surgery-only group. An editorial (*Lancet* 2001, **358**, 1285–1286) stated that since local recurrence is painful and debilitating "its prevention is an important therapeutic endpoint".

The authors stress that it would be 'unsafe' to conclude that radiotherapy does not improve overall survival, partly because the regimes used in these old studies were not optimum. For the future, analysis of studies using safer radiotherapy techniques and systemic chemotherapy will be needed.

"Results from this systematic review suggest that further improvements in survival are achievable, but that they will be of only moderate size and thus large-scale participation in well-designed, randomised trials is needed to reliably detect, or refute, any further benefits," the authors conclude.

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Psychological support for cancer patients

Group support sessions for women with advanced breast cancer can significantly lower their anxiety and depression, according to leading psychiatrist Dr David Spiegel (Stanford University School of Medicine, Stanford, CA, USA). He said that women who attended a group were less likely to suppress their emotions and better able to manage them.

About a third of women with metastatic breast cancer meet criteria for posttraumatic stress disorder (PTSD), he said. They have the same rate of intrusive thoughts, nightmares and flashbacks as victims of sexual assault.

Depression is also common and 20% of terminally ill patients are severely depressed. However, depression in cancer patients often goes untreated.

He described the so-called supportive expressive group therapy to delegates at ECCO-11 (Lisbon, Portugal, October 2001). It aims to help patients build a new network of social support, to encourage expression of emotion, which is seen as an important trigger for action and a means for stimulating support, to detoxify dying and to fortify families.

Cancer patients often feel isolated and removed from the normal flow of life. Friends and family may not know how to address it. Group members have common problems and being able to help each other may give meaning to tragedy. The groups provide a forum to talk about fear, pain and concerns for the future. Many feel less frightened and alone because others around are in the same situation.

"IT HELPS TO LOOK INTO THE ABYSS"

An initial concern, Dr Speigel said, was that patients who saw friends in the group die would be made worse by the meetings. "We found this not to be the case," he said. Making death familiar seems to be helpful. "It helps people if they can look into the abyss," he said.

"If you're taking death seriously, you take life seriously," he said. Groups often spur people on to re-order their priorities; perhaps quitting a job to spend more time at home. One patient's daughter rearranged her degree course so that she could graduate from law school before her mother died.

There is strong evidence that support groups reduce scores of anxiety, depression and pain, he said. The evidence for a survival benefit is still equivocal. One possible mechanism is through the hypothalamus–pituitary axis. Dr Speigel said that five papers in the last year have linked cancer progression with elevated cortisol levels.

Familial factors "have little effect"

Familial factors make only a minor contribution to susceptibility to cancer, say Swedish researchers (*Lancet* 2001 **358**, 1696–1698). They matched more than a million cancer patients on the Swedish Cancer Registry with healthy controls from a national database.

Cancers of the eye, testis, Hodgkin's disease and thyroid had high familial indices of more than 6. Overall, though, familial factors "seem to have a minor effect on cancer susceptibility in general," the study concluded.

Its strength was the number of cancer cases, 1 283 047, included. The limitation was its inability to distinguish between heritable genetic effects and environmental factors as causes of familial aggregation of cancer. However, previous studies have indicated that family environment is unimportant except for cancers of the lung, cervix and uterus. Further, the researchers say, "Our study contains different generations and thus different exposures (e.g. cigarette smoking and shared reproductive and dietary risk factors for cancer differ between the generations), and this fact decreases the environmental influence."

EORTC 'is most active group'

EORTC is the most active co-operative group in the world, according to a survey by 3 Italian cancer specialists. Europe conducts most phase III studies; North America most phase I work, they found.

They identified 3,247 clinical oncology papers reporting phase I, II and III studies and published between 1995 and 1999. The survey was restricted to the 25 countries with at least 10 studies meeting the restriction criteria. It was presented at ECCO-11 (Lisbon, October 2001).

Overall, the US accounted for more than a third (37.7%) of the papers, with Italy (at 9.8%) the runner-up. The UK (8.5%), Japan (6.9%) and France (6.3%) were next.

Dr Francesco Grossi (University of Udine, Italy) said that overall the results were as expected, except, 'We were pleasantly surprised by Italy.' He pointed out that Italy has significantly more physicians than many other developed countries: 'It is likely that Italy's performance may be a reflection of the number of physicians involved in cancer treatment.

Detection of occult cells in bone marrow

Detection of occult metastatic cells in the bone marrow of breast cancer patients offer "intriguing clinical opportunities", German commentators say (*Breast Cancer Res* 2001, **3**, 285–288). Dr Stephan Braun and Dr Nadia Harbeck say that current detection strategies will allow improved tumour staging, therapeutic targeting and, for the first time, the possibility to monitor the efficacy of adjuvant systemic therapy".

About half of breast cancer patients with stage I to III disease will develop metastatic disease, despite resection with tumour-free margins. In up to 40% of these patients, cancer cells can be detected in the bone marrow at the time of primary surgery, using immunocytochemistry.

They call for "concerted international activity" to implement available standardised immunocytochemical procedures, which could then serve as a gold standard with which to compare novel diagnostic approaches. "Further clinical studies that apply the available methodological improvements are urgently needed," they conclude.

EUROFILE

Small projects given reprieve in revised Framework

Plans by EU Research Commissioner Philippe Busquin to create larger research networks at the expense of smaller projects have been watered down by European Union research ministers. At a meeting in Brussels in December 2001, ministers agreed a common position on the Commission's proposals for the sixth Framework Programme for Research and Technological Development, covering mechanisms and funding for both the main research programme and Euratom (the nuclear energy programme).

Framework programmes were set up to fund European research activities and co-ordinate them with and across member states. The sixth Framework started with an ambitious aim: to create a European Research Area strong enough to compete with the research might of USA and Japan. The goal is to allow unfettered mobility of researchers and to provide support at EU level for large-scale research infrastructure.

Human resources in European research and development have been a cause for concern for many years, both in the size of the workforce (particularly in industry), the 'brain drain', and in the decreasing numbers of young people attracted to research careers. The new plans for the European Research Area set out to tackle this, particularly by encouraging a 'reverse brain drain' from countries with a less developed research capacity.

The proposed sixth Framework programme has already run into criticism from many quarters, including Eastern European 'accession' countries, for discriminating in favour of large scale projects and hence favouring countries with a larger science base. Until it was announced, EU research funding had supported large numbers of relatively small projects, creating networks that linked both member states and those in the 'accession' countries. Even so, it was difficult for accession countries to compete for funding. The new proposals would have made it virtually impossible for medical researchers in Eastern Europe to succeed in their grant applications.

"It took us more than 2 years to acquire the skills needed to write a good proposal," said a scientist from Ljubljana, Slovenia, at a meeting in 2001. "The changes (initially) proposed in the 6th Framework will force us to start again from scratch." Research ministers confirm that these were the kind of arguments which convinced them that major changes were needed—away from continent-wide research networks and in favour of continuing to fund smaller projects.

"WE WANT TO AVOID A SHOPPING LIST OF DISEASES TO SUPPORT"

The new Framework will have €17.5 billion to allocate between different research areas, including life sciences. Allocation of the funds has been hotly contested. Parliamentarians, and many in the scientific community, felt there was undue emphasis on genomics to the exclusion of more traditional approaches to disease, and over 300 amendments were made to the Commission's original proposal when the European Parliament voted on the plans in plenary session in November 2001. MEPs voted to allocate €1200m to research into major diseases, including €400m for cancer. However, even Commissioner Busquin has acknowledged that this is small fry: "The European programmes only represent a few percent of funding for cancer research," he said recently.

Given that the pool is small to begin with, Commission officials are unhappy with the Parliamentarians' long list of diseases to be supported. "We want to avoid a shopping list," said one, "or there will be a problem of not having enough money for each disease."

But a shopping list they look likely to get, both in traditional diseases and in genomics. As Italian MEP Gianfranco Dell'Alba said during the debate, diseases like Alzheimer's, Parkinson's, cancer and cardiovascular disease are all waiting for new research efforts. Attacking colleagues who had announced their opposition to stem cell research, he said, "Since Galileo, scientific progress has always fought against the established order. Even if Parliament votes against this report, progress will not stop, knowing that millions and millions of human lives are in danger, threatened with death, yet still with the possibility of cure or effective treatment through the use of new technology."

The research ministers' meeting in December 2001 was the first time that a qualified majority vote has decided the fate of a Framework Programme. There were attempts to block agreement—Ireland sought to ban EU funding for any research resulting from the use of embryos and the creation of stem cells from human embryos, for example, but the voting rule meant that they had no chance of stalling progress.

"IT TOOK US 2 YEARS TO LEARN TO WRITE A GOOD PROPOSAL"

The next step will be for Parliamentarians to vote again, at Second Reading, which will take place in the spring. Research ministers believe that they are likely to accept the new-look Framework. If this is the case, the first calls for proposals can be made before the end of 2002.

"The fact that major diseases such as cancer have been included is a step, but only a small step, in the right direction," said Professor Bill Gullick, University of Kent at Canterbury, UK, and President of the Federation of European Cancer Societies. "It will be important to ensure that the money that has been allocated is used effectively for real cancer research and not to substitute for inadequate funding for cancer treatment."

Mary Rice
Brussels

Biological imaging: time for a paradigm shift

Biological imaging could be the basis for a paradigm shift in the three-dimensional treatment of tumours, according to Dr Chen Chui Ling (Memorial Sloan Kettering Cancer Center, New York). Speaking to delegates at ECCO-11 (Lisbon, Portugal, October 2001, Abstract no. 23), he said that dose painting of tumours, which allows radiotherapists to 'paint' or 'sculpt' the tumour in three dimensions, is now a reality. "We can deliver any intensity pattern within the tissue, with intensity modulated radiotherapy (IMRT)," he said.

"WE CAN DELIVER ANY PATTERN WITH IMRT"

Already this means that, for prostate cancer, for example, high doses can be given to the main bulk of the tumour, with reduced doses in the urethra and rectum. But in future the idea will be taken further.

Recent advances with CT, MRI and ultrasound now provide biological information: the function, physiology and molecular aspects of tumours including their genetic make-up and phenotypic expression of genes. It is no longer anatomical or structural information alone. Images can be integrated to define the biological target, so that, in theory at least, the highest doses could be given to the most active parts of the tumour. Again in prostate cancer, elevated choline and citrate levels have been shown to give an indication of the highly proliferative part of the tumour. The goal is treatment "that conforms to the disease in multiple dimensions," he said. "Perhaps in 20 years' time we will not only have physical conformality, but biological conformality."

Towards a virtual European Cancer Institute

A virtual European Cancer Institute has been proposed, to set the standards for a European Cancer Control Plan, the International Union Against Cancer (UICC) has announced. A meeting in Paris, hosted by the Institut Gustave-Roussy and the Centre Léon Bérard, concluded that the Plan was to be based on a "multidisciplinary, transveral and innovative approach".

The Paris meeting was the second step of EuroCan, a UICC initiative to stimulate the development of national cancer control plans in Europe. UICC Secretary General Professor Stener Kvinnsland said, "There is a need for dialogue and collaboration between the different providers of cancer care to promote cancer control plans in individual countries.

"The sharing of expertise in developing cancer control plans is therefore required. This need has also been recognised within European countries."

The meeting discussed existing cancer plans in European countries, and what could be learnt from them. The final European Cancer Control Plan is to be a "vast plan with the regional focus according to the different health care systems in Europe," the UICC says. The European Commission is expected to promote effective use of resources and collaboration among individual Member States' activities.

Involved organisations include the Association of European Cancer leagues, the Organisation of European Cancer Institutes, the Federation of European Cancer Societies, the World Health Organization and the International Agency for Research on Cancer. The implementation of the proposed European Cancer Control Plan is to be discussed at the 18th UICC International Cancer Congress (Oslo, Norway, 30 June–5 July 2002).

BRCA mutation-profile in Germany

Researchers have established a *BRCA1*/*BRCA2* mutation profile for the German population (*Int J Cancer* 2002 97: 472–480 which will aid decisions for or against molecular diagnosis. The data also provide strong evidence for further predisposing genes.

The German Consortium for Hereditary Breast and Ovarian Cancer analysed the entire coding sequences of *BRCA1* and *BRCA2* for 989 unrelated patients from German breast/ovarian cancer families. They found a total of 77 *BRCA1* and 63 *BRACA2* deleterious mutations in 302 families.

Families with both breast and ovarian cancer were at highest risk of carrying mutations. Of those with 2 or 3 females with breast cancer but only a single or no premenopausal case, mutations were detected in 10% or less cases for both genes.

Priority-setting by committee

Decisions made by a committee drawn from different interest groups have "some inherent moral force," Canadian researchers say (*Lancet* 2001 **358**, 1676–1681). They argue that the decisions of such committees are transparent and public and any discrimination can be addressed by the courts.

The Cancer Care Ontario Policy Advisory Committee for the New Drug Funding Program is comprised of researchers, providers, administrators, patients and the public. The researchers conducted a qualitative analysis of 14 decisions made over 3 years. They analysed documents, interviewed committee members and attended committee meetings.

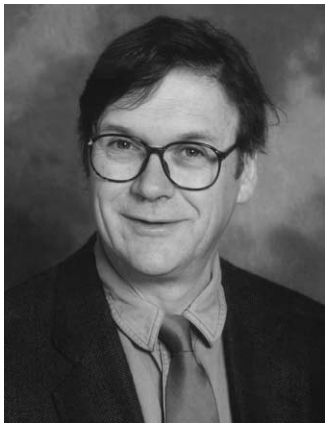
The committee embarked on a complex decision-making process when deciding priorities for funding cancer treatments. Published evidence of benefit was the primary information used, and cost-effectiveness played only a limited part. When the committee did not have sufficient resources to fund a drug they approved, they appealed for budget increases. These were granted twice during the study period.

In primarily private systems such as in the USA, they say, there is no democratic political mechanism for healthcare priority setting and rationales are often implicit.

However, a commentary (*Lancet* 2001 **358**, 1660) notes that trastuzamab was widely available to American breast cancer patients within months of the demonstration of its value, whereas UK patients continue to go without. "Public bodies will often reach conclusions that substantially the same as those that are reached informally in more 'private' systems. They just take longer to do so," it says.

INTERVIEW

Dr Tim Hunt is Head of the Cell Cycle Laboratory at Cancer Research UK, formerly Imperial Cancer Research Fund. In the 1980s, he discovered the first cyclin molecule and he went on to establish the role of cyclins in the regulation of the cell cycle. He was recently awarded the Nobel Prize for Physiology or Medicine for this work, an honour he shared with Sir Paul Nurse and Lee Hartwell.



Dr Tim Hunt

Where did you train?
I studied natural sciences at Cambridge, took my PhD in biochemistry there, and afterwards went to work with Irving London in the Department of Medicine at the Albert Einstein College of Medicine in the Bronx, New York. I had been pro-American from childhood, perhaps because after the War, kind American scholars used to send food parcels to the family.

Who inspired you?
I grew up in biochemistry, and at the time, Francis Crick was the leading light of the Cambridge community. He was a fantastically clear thinker, original, and generous with his time. He often sat at the back of seminars, and asked lots of questions when he did not understand properly. Jim Watson did him a disservice when he said that he had "Never known Francis in a modest mood". That may have been true earlier on, but 20 years later, it wasn't my experience at all.

Did medicine appeal?
I did think about studying medicine, but although there were doctors, physiotherapists, pharmacists and an almoner in the family, I was far too feckless and irresponsible.

Why did you choose to work in the field of cancer?
I didn't. I'm a basic scientist and I originally set out to study the control of protein synthesis, with an eye on the control of cell growth. We know a lot about growth factors, but we still do not really understand how they make cells grow. This, basically, is what I was looking at when I stumbled across the cyclins, and I never did find out about the control of protein synthesis.

Might you have done something else altogether?
I was always interested in science and knew I wanted to be a biochemist before I left school. I was fascinated by the pathways and cycles, and how they were regulated, although I suppose this would be regarded as old hat today.

What has been the highlight of your career to date?
The discovery of cyclin was a real turning point. It was amazing. I knew at once that I was on to something very important. The discovery was much more exciting than winning the Nobel prize, for which it still seems to me that I was a peculiar choice, and just very lucky.

. . . and your greatest regret?
I'm not a regretful person. And I have a terrible memory.

If you could complete only one more task before you retire, what would it be?
Scientifically, I'd like to go back and answer my earlier questions on cell growth. More generally, I'd like to do something about the state of scientific education, particularly in schools because that's where the roots are put down. But even medical education is apt (for good and understandable reasons) to be anti-scientific. If I could help in some way, I would.

What is your greatest fear?
I don't think I'm terribly fearful either.

What impact has the Internet had on your working life?
Absolutely huge. I've always been keen on computery things and use the internet all the time, particularly for searching the scientific literature, and communicating with people by e-mail. Also for buying books.

How do you relax?
I like eating and I'm fond of cooking. I do most of the cooking at home and I have a huge number of cookery books. I don't do experiments myself any more and I suspect that cooking is a kind of substitute.

Who is your favourite author?
I like poetry and philosophy, but have a short attention span and hardly read any novels. I'm fond of magazines and my favourite writer is Jonathan Meades, who until recently was the restaurant critic for *The Times* on Saturdays. He gives wonderful descriptions of architecture and food. Also, the late Richard Olney, whose recipes are perfect examples of experimental protocols: precise, accurate, clear.

What do you wish you had known before you embarked on your career?
Nothing, really. I've never had to made a career decision to speak of; I've just followed my nose and taken jobs when they were offered. The curse of young scientists today is having too many options.

What piece of advice would you give someone starting out now?
Personal interactions are much more important in science than many people realise. It is much better to work with someone you like and respect than with someone rich and famous.

What is your greatest vice?
Laziness and procrastination. I'm grateful that the evil day when I got a proper job (a lecturership) was delayed so long. And getting tenure felt like a death-sentence. In fact, I'm rather against tenure for young scientists; it tends to remove a certain spur to action and have a stultifying effect on their research. I'm not sure when scientists stop being young, either.