A quiet revolution

Alberto Costa* ■ GUEST EDITOR

Every two years, doctors specialising in breast cancer gather in St Gallen to discuss developments and update guidelines on adjuvant therapies. It is always an important conference, but its conclusions tend to be measured rather than headline grabbing.

St Gallen 2005 appeared to be much in the same vein. Yet on reflection, it is clear that in its own quiet way it signalled that a revolution is underway and that breast cancer treatment will never be the same again.

Weighing up the latest evidence, the conference concluded that every breast cancer should be characterised according to eight elements: its size, histological type, grading, hormone receptor status, lymph node status, proliferation index (Ki67), cErbB2 status and the presence or absence of peritumour vascular invasion. Each of these eight parameters of breast cancer is independent of the others, which means breast cancer comes in 64 (8x8) different variants.

The implications of this are very far reaching. The whole concept of breast cancer as a single disease is now dead, and we therefore need to make fundamental changes in the way we approach treatment decisions. For a start, the traditional TNM classification can no longer be considered an adequate guide to treatment, because it provides information on only two of the eight parameters of significance. The value of cytological examination has also been brought into question, because all it can tell us is that we are dealing with a breast cancer.

Many treatment dogmas will also need re-examining. For instance, is radiotherapy always needed after conservative surgery? What if you have just operated on a 70-year-old patient, for a very-low-risk tumour – 1 cm in size, no lymph node invasion, grade I, 90% oestrogen-receptor positive, 5% Ki67, no vascular invasion and cErbB2? It may take the patient two hours by bus to reach her nearest radiotherapy centre and another two hours home again. Is six weeks of daily radiotherapy really worth the time, energy and cost in this case?

Recognising how complex and varied breast cancer is also vindicates the many voices who have been calling for breast cancer to be treated in specialist units by teams comprising a surgeon, an oncoplastic surgeon, specialised pathologist, radiotherapist, medical oncologist and breast care nurse. Given what we now know, it would be utterly irresponsible to continue to treat any patient outside of such a specialist setting.

*Fondazione Maugeri, Pavia, Italy, and Centro di Senologia della Svizzera Italiana, Bellinzona, Switzerland

Peter Boyle: the man behind the statistics

Marc Beishon

As a young epidemiologist, Peter Boyle once had to give a talk on trends in smoking-related cancer, having lost his father to the disease that same morning. Now head of the IARC, his great strength is an ability to inject a sense of the reality behind the statistics his staff work on every day, and a sense of outrage at the inequalities they reveal.

Peter Boyle can't quite believe he's heading one of the world's foremost cancer research organisations. As he says, for a career epidemiologist and statistician, there are few more prestigious posts than director of the World Health Organization's cancer body, the International Agency for Research on Cancer (IARC).

It's all a far cry from his formative years in one of Glasgow's infamous inner-city areas. However, Boyle's credentials fit the bill, from earlier research work at the IARC itself in the 1980s to a long spell at the European Institute of Oncology in Milan, where he rose to international prominence with work that included reassessments of the European Code against Cancer and developing a cancer atlas for the European Union.

What stands out is an empathy with the plight of millions facing cancer in the developing world, and a determination to help improve their lot. As he took control of the IARC last year, the World Health Assembly (the supreme body of the WHO) drew up its first ever resolution on cancer prevention and control, which was adopted this year. It has also introduced the Framework Convention on Tobacco Control. Both are in line with Boyle's aims for the IARC and with his long-standing interest in addressing health inequalities (as well as building on his considerable track record in tobacco research).

"The issue today for cancer is the developing world," he says. "When the IARC was formed 40 years ago, cancer was a disease of Western Europe, North America and Australia – now the majority of new cancer cases are occurring in low- and medium-resource countries. These countries are facing a triple whammy – chronic disease is increasing, there is a high background of communicable disease and they don't have the resources to cope with the rising tide of the cancer burden."

With the growing world population – 6.5 billion now, rising to 9 billion by 2040 – the percentage of older people will grow and cancer rates are set to explode. On his computer at the IARC's headquarters in Lyon, France, Boyle has a programme that shows how the population is

GEORGES MOLLON

"All my career I've tried to grasp the clinical side rather than just the numbers"

With the prime minister of India, Manmohan Singh, earlier this year. IARC is working with partner organisations in Mumbai, Trivandrum, Hyderabad and Jaipur on a range of screening trials in cervix, breast and oral cancer

growing and ageing in China. As he brings up each year in the decades to come, the ageing effect is quite dramatic.

The figures have huge implications, yet presented in this neat digital form, they look somewhat spooky and divorced from reality. This a perception that Boyle is very keen to break through. "I still miss Milan because the European Institute of Oncology was based in a hospital and there are always patients and their families milling about – the reality was there. When I came to the IARC I reminded the staff here that cancer is affecting humans and not just laboratory mice – a few said 'hooray' and some said, 'Goodness what's this?'"

Since assuming the director's post – an elected position voted for by the IARC's Participating States – Boyle has worked quickly to sort out several other more pragmatic issues. One was to address criticisms that the procedures to resolve conflicts of interest in its famed Monographs series, which evaluate the carcinogenic risks of various agents, were not transparent enough. Another was to simplify and improve the structure of the IARC – out has gone some 25 team reports on the agency's work at director level; in has come five scientific 'clusters' linking, for example, epidemiology with biology, and pathogenesis with prevention.

The key role of the IARC, says Boyle, is to develop unique work programmes that cannot be conducted at national level. "Our descriptive epidemiology, very influential in the developed countries, is now having a huge impact in the developing world, and the Monographs programme that evaluates carcinogenic hazards is essential and frequently the basis of environmental health legislation at country level." Other highlights are EPIC (European Prospective Investigation into Cancer and Nutrition – a large multi-centre cancer study), the TP53 mutation database, and a major project on cervix cancer screening in rural India. And a common thread now, he adds, is "integrating epidemiology with a laboratory component – mainly genetic".

With some 300 staff, IARC is a sizeable concern, and in Boyle it has a director with long experience of applying such analysis to real world problems from an early stage of his career.

Boyle was one of the first students to read for a brand new statistics degree at the University of Glasgow, and initially his ambition was to be a schoolteacher. It was by chance that a project he selected – a study on the risk factors for post-operative pain – got him involved with healthcare and he moved to Glasgow's Western Infirmary as a doctorate student. After various statistical analyses and consulting work he got the chance to help organise the West of Scotland's cancer registry and projects around it, such as clinical trials, with a particular focus on epidemiology.

"I was hooked – I liked the work very much, but all my career I've tried to understand what the clinical side of the problem is, rather than just looking at the numbers. It would have been a waste for me as a statistician to just sit in a room and wait for someone to give me data to analyse – although such pure academic research is fine for some people. I've never been involved in actual patient care but I have constantly been exposed to clinicians and they accept you if you understand what they are talking about and can help them."

He recalls a time in the cancer registry, laboriously writing down age-specific cancer rates – 0–4, 5–10, up to 85+ – on forms in the days before desktop computers. "There was a uniformity. You knew that say at age 50–54, if you had 50 cases in one year you wouldn't get 3,000 the next, as you might with an epidemic infectious

disease. It meant we could investigate underlying mathematical structures and see what was going to happen – and make the big jump, to why it was happening."

This drive was to propel him on a journey that would lead him to work among the elite names of epidemiology – Richard Doll, Richard and Julian Peto, Brian MacMahon – names he recites with almost as much reverence as those of Glasgow Celtic's European Cup winning team of 1967.

Laying his hands on Scottish cancer mortality data from 1911, he updated the registry information, demonstrating the huge and predictable changes in tobacco-related cancer over time. "I submitted a paper to a big epidemiological association meeting in Edinburgh and got on the programme," he says. "On the morning of the day I was due to speak, my father died from lung cancer – he was a smoker most of his life – and in the afternoon I gave a talk on the trends of smoking-related cancers in Scotland. That was tough – but it was reality."

Boyle was then to leave Scotland, so far for good, with his wife Helena and his first child. In a roundabout way, via a training fellowship at the IARC, he found himself as an assistant professor at the departments of biostatistics and epidemiology at both the Harvard School of Public Health and the Dana-Farber Cancer Institute. "After an hour I realised that the cleaners knew more about epidemiology than I did – I didn't have a clue about the fundamentals."

And the biostatistics group, he says, "had written the book about how you do clinical trials – and may well have been the best group of biostatisticians ever assembled. It was the attention to detail – data quality, model selection, examination of interactions and ensuring the randomisation worked before coming up with answers. Looking back it seems obvious, but it wasn't then."

The challenge is not just to conduct rigorous randomised controlled trials, which for so long were considered the gold standard in medicine. As Boyle points out, in public health work evidence may need to come from a variety of both 'hard' and 'soft' sources. "One of the first things I did here was create a tobacco unit – there had never been one at the IARC – and we want to now write a series of handbooks on the scientific evaluations of tobacco control recommendations.

"If we were looking at say a substance such as formaldehyde, which we do in our Monographs, we have a choice of maybe a hundred peer-reviewed papers in the literature – but a lot of work on tobacco interventions that, say, try to stop children smoking are not published in the same way – or not published at all. The level of information you can use to make decisions is weaker and is more sociology and psychology than hard-nosed science."

Developing methods of sufficient scientific rigour that consider 'softer' evidence is certainly needed, particularly to identify interventions that target health inequalities. As Boyle mentions, measures for getting people to quit smoking have often been more successful with well-off people with more motivation and better access to resources – potentially widening the health gap (his home country of Scotland being a prime example).

The need to focus on the real issues was brought home to Boyle in the US by John Cairns, "a father figure of biology". "He said that from time to time you have to look at issues, not just uniquely focused scientific questions," says Boyle. "John got me to look at a paper in *Science* that said that since the introduction of the cancer chemotherapy programme in the 1950s, it was saving 150,000 deaths a year in the US. I looked at the data and put it together with what we knew about outcomes and found that the number of deaths saved a year was 15,000 – maximum. We did get a reply in *Science* – but

"After an hour I realised that the cleaners knew more about epidemiology than I did"

they left off the tag that 10,000 medical oncologists were preventing only 1.5 deaths each a year."

Boyle managed to escape intact from the US after this, and faced with a choice between working in Glasgow or the IARC at Lyon, chose the latter. He directed a programme called Search – Surveillance of Environmental Factors Related to Cancer in Humans – a series of case-control studies across several centres on subjects such as children's brain tumours.

Then in 1991 he was invited to head up the department of epidemiology and biostatistics at the European Institute of Oncology in Milan – in fact he was the first employee at the then fledgling outfit, one of the many brainchilds of famous cancer surgeon Umberto Veronesi.

Boyle mentions several highlights of his long tenure at the institute. One was being able to continue research interests such as the link between pancreatitis and pancreatic cancer – with various collaborations he helped the work through all the way to identifying a gene from an initial case control study.

"Veronesi was also very generous in allowing staff to be involved in bigger projects – and I got a lot of exposure in the European Cancer Experts Group." One of Boyle's inputs to this group – which is a European Union meeting of experts – was a document informing a consensus meeting on tobacco. Approved by the then European health commissioner, Padraig Flynn, and after a good deal of reworking, it led to the European tobacco directive on the content of cigarettes. "I was invited to the European Parliament for the final approval vote – that was public health in action," says Boyle.

He pays particular tribute to subsequent health commissioner David Byrne, who saw both the EU tobacco content and advertising directives through. "I was very close to David – he was magnificent despite having to contend with major dramas such as BSE ['mad cow disease'] and other food scares. He wasn't a public health man by training but could see what a huge impact tobacco control could have in Europe and he put his career on the line."

Tobacco is a big preoccupation for Boyle. He is lead author of the book *Tobacco: science, policy and public health* (OUP, 2004) – and he is naturally worried that this century will turn out to be even more grim "There are currently about 1.2 million cases of lung cancer around the world – if nothing changes this will rise to the same number in China alone by 2030. We will be swamped by smoking-related disease." He has high hopes for the WHO tobacco framework, although time is clearly short even for a global organisation to make an impact.

As he adds, public health professionals will only see results through the often brave action of politicians, such as David Byrne and others on the tobacco front in places like Ireland, Italy and New York. Boyle's engagement with movers and shakers at European – and now world – level have certainly given him insight into the art of the possible and the politics of running organisations.

That insight was quickly tested at the IARC, when EU funding streams for several cancer projects such as EPIC were cut off, and he's had to provide bridging monies while alternative sources were sought.

He also inherited an attack on the integrity of the IARC over possible conflicts of interest on regrading the status of certain carcinogens. "We couldn't put our finger on an instance where a meeting was deliberately hijacked by undeclared vested interests," says Boyle. "Classifications can go up and down as more evidence becomes available." To silence the critics, however, the IARC has now created a new category of 'invited specialists,' where any with conflicts are not allowed to write drafts, vote or

"One of the first things I did was create a tobacco unit – there had never been one at the IARC"

chair working groups, and all names are published on its website.

Inevitably he is well plugged into the politics of the European cancer community – a particular concern is that there are rather too many obstacles at present to achieve the kind of unity that would maximise European resources. "Things are still too national – there are huge barriers to mobility within Europe," he says. "It's not so much at the administrative level, but cultural – it's very difficult to recruit a 45- to 50-year-old professional who may be at his or her most productive, when they are tied down with children's education and other factors. It means that, for example, if the head of the National Cancer Institute in the US wants to set up a national proteomics centre he'll get the cream of 280 million people to work in it – in Europe with 500 million people, the UK, Germany, France and so on will all set up their own."

Further thoughts will no doubt arise from a major grant from the European Commission that Boyle has been awarded – for a feasibility study on co-ordination of national cancer research activities.

On the vexed question of a European wide cancer society, Boyle feels that FECS (the Federation of European Cancer Societies) was a great idea at the time – but it now suffers from being an organisation whose members are other membership bodies. If it can evolve into a society with more individual representation it would probably assume a higher international profile, he feels.

And while recognising that the recent European breast cancer resolution has raised the profile of this disease, he is concerned that the fight against cancer should not be fragmented too much – "We have to find ways of unifying interest groups," he comments.

Integration across a broad range of cancer research issues is certainly Boyle's aim with the IARC's cluster structure. "One of the great advantages we have is that we have all groups here – genetics, epidemiology, biostatistics and so on – which you don't have in most other institutes." As an example he cites the genetics and epidemiology cluster, which has researchers with a spectrum of strengths in the two disciplines, plus laboratory expertise. "That cluster works together very closely – we collect the data and the correct biological material in well-designed epidemiological studies, and it is analysed in the lab in a state of the art way to be interpretable in terms of what's happening in the population."

GEORGES MOLLON

Boyle's 300 staff, at the IARC headquarters in Lyon, cover a wide range of cancer-related expertise, including epidemiology, pathology, genetics and biostatistics

Boyle's focus is now of course on the world cancer stage, which is guiding where this expertise is targeted. "If we want to make an impact we have to focus more on the low- and medium-resource countries – while not neglecting the developed countries, where we can still help.

"For example, there is an epidemic of oral cancer in Central and Eastern Europe – the mortality rate has gone up 10 fold in Hungary in the last 30 years. We have got to compare risk factors there with Western Europe, where the mortality rate has not gone up, and we're not only interested in alcohol and tobacco as risk factors – is there a genetic cause too? These are the sort of big studies we organise."

But it's clear too, he adds, "that in the poorer countries effective prevention is going to be much cheaper than treatment and we need to develop appropriate strategies." As such, screening work is assuming a higher profile. "For example, we now have results from ten years' follow-up of a screening study of oral cancer in Kerala, India, which shows mortality reduced by one-third among those at high risk. We also have a randomised trial of 120,000

Getting results can depend on brave action by politicians such as David Byrne on the tobacco front

women in rural India for cervix cancer. It's a huge and extremely important study and we have finished the first round of screening – and again, while no results are yet available we are extremely pleased that we managed to treat over 80% of women who we thought were positive. That's so different from what goes on in poor rural settings at present."

The cervix screening work is backed by the Bill and Melinda Gates Foundation, which Boyle says is one of the major funding sources for projects of this nature. He adds that such work also needs to take account of local conditions – "We in the West may have been guilty of identifying what we perceive as the priorities and applying a Western solution. That may not be the way to go."

In the cervix cancer programme in India, for example, a 'low-tech' visual inspection is also carried out to 'see and treat' immediately – as many women would simply have been lost to further clinic follow-up. As part of a consortium of public health agencies, the IARC has also launched a toolkit for implementing cervix cancer screening, while Boyle, on a recent trip to India, was invited to meet prime minister Manmohan Singh – "He is aware of health and poverty issues."

While the low- and medium-resource countries have pressing priorities, Boyle is also struck by just how much disparity is present in the developed world. In the IARC's cancer mortality atlas of Europe, which covers the expanded European Union, some of the worst figures for lung cancer do come from the poorer member states. "But the highest rate of all is in Glasgow, where 70–80% of the population are in deprivation categories six and seven."

He mentions a study on breast cancer outcomes in Scotland that found a big gap in survival rates between well-off and poor people after adjusting for prognostic and treatment factors. "We have to find out what's driving that – there's something inherently unfair in a poor person having a poorer survival outlook compared to a more well-off person with identical disease. It's the sort of inequality that leaves you really cold." He's also acutely aware that in some advanced countries – the US, for example – women from some sections of the community are also still presenting with advanced disease.

As he adds, it's only been in recent years that these differences have been visible through population indexing techniques. It all adds to the complex jigsaw that makes up the risk factors and risk determinants for cancer, and Boyle feels that deprivation is a critical factor that is not receiving enough attention.

Boyle's broad understanding of the cancer research spectrum has put him well up journalists' contact lists for comment on topics such as risk factors, screening and treatment that tend to flood the media. As he notes, there are some hundreds of risk factors for breast cancer alone, and there are many institutes sending out press releases – a recent one from the IARC itself concerns a study showing that vegetables and fruit are not protective against breast cancer. And a current IARC study on mobile phone use is bound to generate great interest.

"It's unfair that a poor person has a worse prognosis than a better off person with identical disease"

While he professes exasperation at some of the more absurd media reports, he points out that sometimes the cancer community has itself to blame. "A particular bee in my bonnet is at meetings where papers are press released to get media attention, but often have many holes in their findings, being suitable only for a poster or short presentation.

"A while back at the ASCO [American Society for Clinical Oncology] annual conference plenary session there was a paper that claimed that PSA testing reduced the mortality rate of prostate cancer – it got huge publicity. I'd seen the paper a month before – and I said at the meeting that using an 'intent to treat' analysis showed there was absolutely no evidence of a protective effect." This publicity machine "is wrong and a disservice" to the cancer community, adds Boyle.

On a personal note, Boyle has certainly proved that it is possible to develop a career away from his roots. His three daughters were educated in Lyon and Milan and are all now pursuing medical careers – the "stream of strange foreign medical people arriving for dinner" over the years being a clear risk factor in their choice, as he puts it. However, his wife Helena did have to give up her career as a maths teacher to look after the family and help the children with their studies.

His great passion is football – he used to play himself and has always been a fanatical Celtic supporter. But Scotland in general is a great reference point. In talks he's spoken of the 'good, bad and ugly' of cancer work in the country, from outstanding progress with a national cancer plan down to the continuing impact of deprivation. He's quoted Voltaire saying, "We look to Scotland for all our ideas about civilisation" – as its model of cancer control is eminently exportable (and there also seems to be quite a lot of Scots making waves in world cancer work). At home in Lyon, he always logs on to the Internet to see the latest news from Scotland.

Looking ahead to achievements for the initial five years of his post at the IARC – and a second term could be on the cards – Boyle says he was first encouraged to set targets, which he has resisted. "In 1985 when Europe Against Cancer was set up, the cancer experts met for the first meeting in Milan and, against a huge rise in cancer rates, they set a target to reduce the number of deaths in Europe by 15% by the year 2000. I saw this published at the time and colleagues and I laughed.

"But through a series of actions on screening, primary prevention and tobacco control there was a 9% reduction in the number of cancer deaths expected." Boyle was in fact lead evaluator for the target by this point. To achieve more than half of that ambitious target was tremendous, he says, and there is plenty of merit in having such goals even if they are not met (and since then the EU has set a new target of a 20% decline in cancer mortality for 2015).

For someone so well versed in number crunching, though, his preference is for a more qualitative approach for the IARC. "If I can increase the quality and relevance of the research we do here, increase prospects for cancer prevention and help improve the situation in the poorer societies, I'll be quite happy."

GEORGES MOLLON

With David Byrne, then European Commissioner for Health, who Boyle says "put his career on the line" to get through the European directives on tobacco content and tobacco advertising

Mutation explains relapse on EGFR products

A discovery made simultaneously by two groups of US researchers may help lung cancer patients who relapse after an initial response to novel targeted therapies.

Scientists have discovered an epithelial growth factor receptor (EGFR) mutation that could explain why non-small-cell lung cancer (NSCLC) patients relapse on the EGFR tyrosine kinase inhibitors Iressa and Tarceva, after an initially good response.

Two teams seem to have raced each other to press with the publication of two papers coming just two days apart.

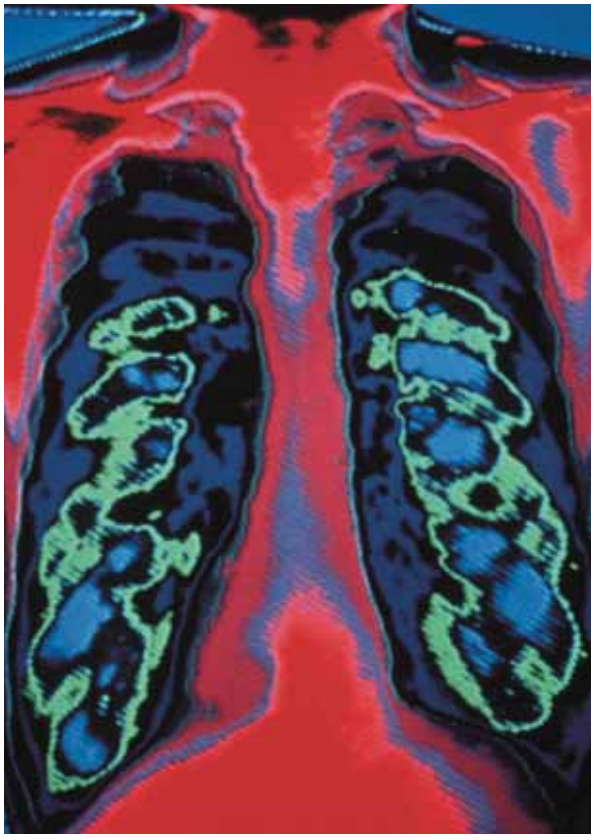
The research could be important for the development of second-generation EGFR inhibitors and could help refine the use of Roche/OSI/Genentech's Tarceva (erlotinib) and AstraZeneca's Iressa (gefitinib), although the latter is facing an uncertain future after it failed to show a survival benefit in the phase III ISEL (Iressa Survival Evaluation in Lung Cancer) study.

A group of researchers from the Memorial Sloan-Kettering Cancer Center had their work published online on February 22nd in *PLoS Medicine*[1], ahead of its print version in March.

The other team, which was led by Balazs Halmos from the University Hospitals of Cleveland, published its research as a brief report in the *New England Journal of Medicine* (February 24th, p786). The results add to findings last year that patients who responded to Iressa therapy had mutations in EGFR that sensitised them to the drug.

The Memorial Sloan-Kettering team discovered the new mutation, T790M, in three out of six patients resistant to either Iressa or Tarceva and confirmed the finding in an NSCLC cell line. The other scientists found T790M in a 71-year-old man who had 24 months of complete remission on Iressa before relapsing.

It is not yet clear how the mutation arose. However, after surveying 150 tumours and reviewing the literature, the Memorial Sloan-Kettering researchers think it is probably extremely rare in NSCLC tumours that have not been treated with either drug. The mutations could either arise de novo during treatment, or else subclones with the mutation could become



HOWARD SOCHUREK / CORBIS / CONTRASTO

[1] *PLoS Medicine* is published by the Public Library of Science – a non-profit organisation of scientists and physicians committed to making the world's scientific and medical literature a freely available public resource.

T790M corresponds structurally to a mutation that commonly causes resistance to imatinib in CML

more prevalent as Iressa/Tarceva-sensitive cells die.

The mutation does not appear to be the only reason for resistance to Iressa or Tarceva. The Memorial Sloan-Kettering researchers found that a further three resistant patients did not have the T790M mutation. They also note that T790M is distinct from the KRAS gene, which is known to cause primary resistance to the products, and EGFR over-expression could also be a source of resistance. The authors of the NEJM paper suggest that the development of a new EGFR mutation shows that the tumour cells remain dependent on EGFR for their proliferation.

Second generation

Understanding exactly how T790M stops cells responding to Iressa or Tarceva could help design second-generation inhibitors. It seems, from crystal structure analyses, which both teams carried out, that an amino acid substitution caused by T790M creates a steric clash so the products cannot bind to EGFR, but the mutation does not stop the receptor from functioning. Therefore, products that bind to EGFR in a different way would be less affected by T790M.

After looking at structural data on the compound, the Memorial Sloan-Kettering team speculates that GlaxoSmithKline's dual EGFR/Her2-targeting anticancer, lapatinib, could have a role in resistant patients, although they note it has not yet been tested in this population. Lapatinib is in phase III trials for lung cancer, although the lead indication is breast cancer.

In a *PLoS Medicine* Perspective piece published with the paper, Gary Gilliland from Harvard Medical School and colleagues say there should be a more proactive approach to developing drugs to tackle resistance. "In vitro screens for mutations that confer resistance to kinase inhibitors are warranted, followed by effort to identify drugs that overcome resistance."

Imatinib parallels

The discovery of the new mutation mirrors the experience with Novartis's Bcr-Abl tyrosine kinase inhibitor, Glivec (imatinib), the authors of both papers note. Knowledge of the mechanisms of resistance – point mutations or amplification of the BCR-ABL gene – has helped develop second-generation products such as Bristol-Myers Squibb's BMS-354825 and Novartis's AMN107. These products bind to ABL in an 'open' rather than 'closed' conformation, leaving them less susceptible to mutations to the binding site. Another parallel with understanding on imatinib could help predict drug resistance in similar products in future. This is because T790M corresponds structurally to a mutation which commonly causes resistance to imatinib in chronic myelogenous leukaemia. "This finding suggests that there are mechanisms of drug resistance common to tyrosine kinase inhibitors that could be predicted from the start," say Jonathan Dowell and John Minna from the University of Texas Southwestern Medical Center in an accompanying editorial in the NEJM (p 830).

The authors of the NEJM study think the research "underscores the need to consider incorporating repeated biopsies into clinical studies of novel targeted therapies." Gilliland and colleagues agree that patients who relapse should have a re-biopsy. "It is clear that data derived from such analyses will be essential to inform approaches to improving therapy for NSCLC and other solid tumours."

Dowell and Minna also note "It will be important to discover at what stage in the pathogenesis of lung cancer EGFR mutations occur." If they are found in preneoplastic lesions, they suggest that patients could be given relatively non-toxic tyrosine kinase inhibitors to avoid the use of chemotherapy.

First published in issue 3033 of *Scrip World Pharmaceutical News* March 2nd 2005.

Fertility: it's up to doctors to think ahead

➜ Emma Mason

Young cancer patients should feel lucky to survive, and stop fussing about their prospects of having children. This attitude, though still widespread, is now being challenged by many patients and doctors, who argue that it is inexcusable to prescribe treatments that could render a patient infertile, without a thorough discussion of all the options.

A Belgian woman made medical history in September 2004 when she became the first mother to conceive and give birth to a baby after an ovarian transplant following her successful treatment for cancer.

For Ouarda Touirat, 32, the arrival of her daughter, Tamara, was a dream come true. The achievements of her team of doctors, led by Jacques Donnez at the Catholic University of Louvain in Brussels, gave hope to hundreds of other women who were facing similar prospects of possible infertility after cancer treatment.

Touirat had been diagnosed with stage IV Hodgkin's lymphoma in 1997 at the age of 25. Before she underwent chemotherapy and radiotherapy, Donnez and his team extracted strips of ovarian tissue from her left ovary and froze them. The cancer treatment cured her Hodgkin's lymphoma, but left her infertile.

In 2003 the frozen ovarian tissue was thawed and reimplanted just below her right ovary. Five months later her menstrual cycle was restored and in January 2004 she became pregnant naturally, without assisted reproduction technology.

In his *Lancet* paper (vol 364, pp 1405-1410), Donnez wrote: "Our findings open new perspectives for young cancer patients facing premature ovarian failure. Ovarian tissue cryopreservation should be an option offered to all young women diagnosed with cancer, in conjunction with other existing options for fertility preservation, such as immature oocytes [egg] retrieval, in-vitro maturation of oocytes, oocyte vitrification, or embryo cryopreservation [freezing]."

However, the medical world reacted more cautiously. Two letters in a subsequent issue of *The Lancet* (vol 364, pp 2091-2092 and 2093-2094) pointed out that it was not yet safe for this experimental procedure to become standard practice. Not only did the treatment have a very low chance of success, but also it was arduous and invasive, there was a risk of the original cancer re-seeding itself from the transplanted ovarian tissue, and important ethical and legal issues needed to be addressed.

The case of Touirat is a good example of

YVES LOGGHE / AP PHOTO

Baby Tamara, pictured here with her parents Ouarda Touirat and Malik Bouanati, was conceived naturally after her mother received pioneering fertility preserving treatment. The procedure, which involves removing ovarian tissue and reimplanting it following cancer treatment, offers hope to many young women, but it is still highly experimental and many safety concerns remain

some of the technical and ethical problems that confront oncologists and fertility experts when treating patients of reproductive age with a diagnosis of cancer.

Many oncologists and patients would agree on one thing, however: it is vital that cancer patients should be given an opportunity to discuss issues and explore options related to their fertility before any treatment is begun that could render them infertile.

The doctor's duty

Sophie Fosså, a urologist who specialises in testicular cancer at the Norske Radium Hospital in Oslo, Norway, sees patients of all ages and believes that it is her duty to raise the issue of her patients' future fertility with them.

"It's very important that as a doctor you consider fertility and fertility-saving treatment options as much as possible. It is important both for the doctor to consider it and for the patient to know that you are considering it," she said. "Doctors have to take a proactive role, especially with the young ones who will never talk to you spontaneously about it. Often, boys and young men will say they don't want to think about fertility, they don't want to take more time out of their lives to go to clinics to give semen samples, they just want to be cured, and then you have to push them to think about it."

Discussing fertility serves another purpose too, believes Fosså. "With a young boy it is giving a very important, indirect message that you believe that they will be cured and life will continue. Many patients don't believe that they will survive, but if you do these things to preserve their fertility you are telling them life will go on. It's very important psychologically for young men to freeze semen."

Antonella Surbone, Head of the Teaching Division at the European School of Oncology in Milan, Italy, and a breast cancer specialist, said that fertility issues are a major concern for young patients. In a 1996 study, patients treated for Hodgkin's lymphoma ranked fertility amongst their top three concerns, along with whether or not they were going to be cured and whether or not the cancer might recur. As such, it is one of

Vickie Maye

diagnosed age 25

On September 11, 2001, as people worldwide watched in horror as two passenger jets smashed into the World Trade Center in New York, Vickie Maye was staring at an X-ray of her chest.

"Right in the centre, extending across my ribs, there was a grey blur, almost like a cloud. Just a couple of hours earlier, a doctor had told me it was 'abnormal'. Two weeks, two biopsies and many sleepless nights later, I was told I had cancer. I was 25 years old."

Vickie is from Ireland but was working as a journalist in Australia at the time, and while her boyfriend, also a journalist, was working flat out on the biggest story in decades, she was having to grapple with a diagnosis of Hodgkin's lymphoma.

"The diagnosis blew me away. It came as a complete shock."

The cancer had only been discovered because the Department of Immigration required a medical examination, including a chest X-ray to rule out tuberculosis, before it considered her application for residency in the country.

Vickie was treated with chemotherapy (ABVD) and radiotherapy, but right from the start she wanted to know about the effect the cancer and its treatment would have on her fertility.

"Fertility was a big issue for me. It was one of the first questions I asked, after was I going to die and was I going to lose my hair. The thought of having no kids haunted me. My haematologist told me that the treatment he was giving me, ABVD, was going to give me a better chance of not being permanently infertile. I knew the chances were good but they couldn't give me guarantees.

"My haematologist was amazing, but his main concern was to get rid of the tumour. While he gave me treatment that had been shown to have less impact on fertility, he simply wasn't clued in on the ins and outs of it all.

Incorrectly tested

"Soon after treatment, I asked my haematologist if I could have my fertility tested. He agreed and arranged the necessary blood tests. When we got the results, two of the three levels showed I was post-menopausal. I was beside myself. He told me to relax, that he would repeat the tests again in a few months. I simply couldn't wait another three months. The stress was too much. So I took it upon myself to see a fertility expert. He told me that to test fertility, bloods need to be taken on day one or two of a woman's period. The samples were taken at the right time and my fertility was found to be normal. The soaring levels previously recorded were simply a result of incorrect timing.

"This was the only issue I had with my treatment: the apparent lack of communication that existed between fertility experts and cancer specialists. While I appreciate that my doctor's focus was to cure me of cancer, fertility was naturally a concern to me in my 20s and should have been addressed appropriately."

Soon after her treatment finished, Vickie returned to Ireland where she now works on the *Irish Independent*. Aged 29, she is in remission, her ovarian function has returned to normal and in July she is due to give birth to a daughter, Mia, conceived naturally without assisted reproduction technology.

"I waited two years, as recommended by the doctors, before becoming pregnant. While I had had fertility tests done, I still had this awful feeling that I would be unable to simply fall pregnant. I imagined I would have to face IVF [in-vitro fertilisation]. It used to haunt me. So she is a little miracle!"

Fertility was a big issue ... the thought of having no kids haunted me

the primary issues that oncologists should discuss with their patients, not necessarily in their very first consultation, but very soon afterwards.

"Oncologists need to know about treatment choices, both in terms of efficacy in dealing with the cancer, and in terms of the degree of toxicity and the effect it might have on the patient's fertility. You have to make a treatment choice, offer a treatment choice, and evaluate whether you are going to give a treatment that has *x* risk of causing infertility versus one that has half that risk. It's inexcusable for an oncologist to prescribe without knowing about the spectrum of toxicity, especially fertility, knowing this is one of patients' top concerns," she said.

Surbone says that both oncologists and their patients need to know three things. "Fertility can be impaired due to factors unconnected with cancer, such as hormonal disturbances, sperm quality, smoking and alcohol; this is still a hypothesis, but fertility may be impaired by the cancer itself; and, fertility can be impaired by the cancer treatment.

"These need to be explained to the patient, although, as an oncologist, I can only look at the third aspect when discussing treatment options with my patients."

Unfortunately, not all oncologists are willing or able to discuss fertility with their patients, and nor do they always communicate with or refer patients to fertility clinics, as Jan's story (below) and the other case studies (pp. 48, 51, 52) show. Jan, from southern Germany, was diagnosed with chronic myeloid leukaemia (CML) three years ago when he was 28. He still feels angry about the way the subject of his future fertility was handled.

"The diagnosing doctor didn't really tell me about impacts on fertility and about freezing semen before starting a therapy – he would have put me on chemotherapy right away. Luckily, I wanted to know all my options before taking any drugs, so I drove all around Germany to receive second opinions from several doctors. One internationally renowned specialist in CML research, who is still my trusted doctor today, calmed me down and said that for CML there was no reason to hurry into any treatment. I should make up my mind first about my preferred therapy, bank sperm and then start a treatment in a few weeks."

Time to consider

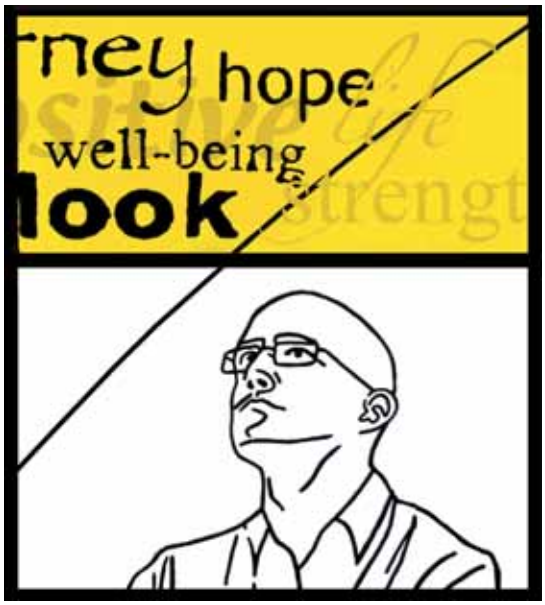
This is what Jan did and he is glad that he took the time to find out. "After receiving a diagnosis of CML, nothing was more far away than thoughts of family planning. But look at my situation today: the treatment works successfully, the illness is currently under control and normal life has returned. I am 31, happily married, in a normal job, and hoping for a long life. It would be devastating not to have had the chance to take precautions to preserve my fertility. This is something young patients have to be made aware of before starting any cancer treatment."

But Jan raises two fears that are worries for patients and their doctors: will the cancer or genetic mutations arising as a result of it or its treatment adversely affect any offspring, and will his own cancer recur while he is trying to start a family with his wife?

Jan's CML is held in check with Glivec (imatinib), a newly-developed drug, which is still being tested in clinical trials. "Even though Glivec has been in use for four years, there is little official data on fertility. I am in touch with more than a dozen patients who have fathered children during Glivec therapy, ignoring any warnings, and all babies seem to be very healthy. But who knows in the long term, and who collects the data?

"Additionally, stopping the drug before fathering would be one option, but who knows that conception would be immediate? Stopping therapy would give my illness an opportunity to proliferate; so this is risky as well. We also don't know whether in-vitro fertilisation will induce

"It's like trying to back a horse without knowing how many horses are running or in which race"



Dan Savage (see also box opposite) created 13 paintings focusing on his experience of cancer, including its potential impact on his fertility. The images were displayed last May at the conference of the Teenage Cancer Trust, for which he acts as an ambassador in the UK

additional risks and strains – for my wife as well as for the baby. We already made one attempt that failed, so we know this way is not the easiest.

"Therefore, we'll have to decide between the risk of conceiving whilst on the drug, the risk of stopping the drug, or the risk of in-vitro fertilisation. All their life, young cancer patients like myself have to decide on uncertainty."

Jan has put his finger on the crux of the problem that confronts cancer patients: it is rare for there to be a treatment option that is clearly the best path to take. Patients and their doctors constantly have to weigh up uncertainties, trying to choose the treatment that is most efficacious while also fitting in with the patients' aspirations for the future.

No sure bets

Sarah Gahan, 42, a breast cancer patient who is now in remission (see p. 52), said: "There are lots of choices, but no obvious right way or tidy decision that can be made, and sometimes the doctors and scientists are as much in the dark as you are.

"My tumour was oestrogen positive, and with this type of tumour the question is whether trying to become pregnant and pregnancy itself might make the tumour grow more. And the answer is that nobody knows. It's like trying to back a horse in a race when you don't know how many horses are running or in which race." This is where good communications and relations between doctors and their patients are vital, so that patients feel that they are able to make fully informed choices about their treatments, with support and advice from a doctor they trust.

Both Fosså and Surbone point out that oncologists need to consider fertility issues when their patients have any cancer where the treatment involves chemotherapy or radiotherapy, both of which can damage fertility either temporarily or permanently, and not only when the cancer is related to the reproductive organs (as with testicular, ovarian, endometrial or breast cancer).

In many ways, the options open to boys and men when confronted with a diagnosis of cancer are easier than for girls and women. Men can have their sperm frozen and the sperm do not suffer too much during the freeze-thaw process. The sperm can then be used at a later date to fertilise a partner's eggs by in-vitro fertilisation, sometimes using intra-cytoplasmic sperm injection (ICSI) to make sure the sperm reaches the egg successfully.

Even for younger boys who are not yet able to ejaculate sperm, there is a possible solution. Fosså said: "Sperm can be extracted under

Dan Savage

diagnosed age 20

Dan, 22, was studying art at Lancaster University when he discovered a lump the size of half a pea in his right testicle two years ago.

"I was actually checking my testicles because a teacher of mine at school had had testicular cancer and he told us all to check our testicles regularly, so I did. The doctor thought it was a cyst, but I pressed a bit harder and he referred me to the hospital. Ultrasound showed it was stage I testicular cancer. I was lucky because I caught it early. I had the operation at Lancaster and then was transferred to St James's in Leeds for chemotherapy.

"The chemo was largely precautionary. The outward appearance of the tumour suggested it was early, but when they dissected it, they found it was quite developed, just on the brink of spreading and they didn't want to take that risk.

"The doctors talked about fertility before they gave me chemo. It came as quite a shock, and I hadn't considered it. It was very sudden from that point on, as I had to go to the fertility clinic twice to provide sperm samples, once three days before I started chemo and once on the very day I started my chemo.

"I think that you should know about fertility issues beforehand, especially as at my sort of age and a bit older you start to think about starting a family, and it's important. I think I'd probably wait a few more years before starting a family, but I would like to have children while I'm still in my 20s."

Dan is now in remission, but goes for regular checks. He was keen to highlight one particular aspect of his experience. "Two months before my cancer was diagnosed I had a swelling of my breast tissue. When you are about 14 or 15 you have that feeling and it is to do with the maturing process, so I thought it was the hormones, but actually it was the testicular cancer. No one has ever mentioned this as a symptom, and it's quite important that people know about it. Had I known, I might not have needed chemo, as the testicular cancer would have been caught months earlier."

It came as quite a shock when the doctors mentioned fertility

anaesthetic, although the success of this is not clear yet, and it's very important for these young boys that you don't over-treat."

Technical challenges

For girls and women, the options are more complicated. The female ovary contains its full complement of eggs at birth. However, techniques for freezing eggs have not been very successful so far, with the egg suffering severe damage during the freeze-thawing process. Therefore, a woman has to have a partner who can provide sperm so that any eggs retrieved can be fertilised immediately, allowed to start developing into an embryo in vitro and then frozen until it can be implanted in the woman when the cancer treatment has finished and she is ready to start a family. For girls or women without partners, this is not an option open to them, nor is it available in many countries.

However, it is possible to freeze and thaw successfully whole ovaries or strips of ovarian tissue. Eggs can be retrieved from the thawed tissue, matured in vitro, then fertilised and any resulting embryos implanted. Or, as the case of Touirat shows, the ovarian tissue can be transplanted back into the woman, although this is at too experimental a stage to be considered a standard option.

Where radiotherapy is part of the treatment, it is sometimes possible to remove the ovaries from the radiation field. Some drugs used in chemotherapy have a less severe effect on fertility, both for men and for women, than others, and it is quite possible for fertility to be restored once the treatment has finished. A common theme amongst the cancer patients featured here

Sarah Gahan

diagnosed age 36

Sarah Gahan, 42, and her husband had been trying to start a family for 18 months without success when she discovered she had breast cancer at the age of 36.

"I found a lump in my right breast, which didn't worry me at all because I'm used to having bumps on me from lipomas [small benign, slow-growing tumours that come from fat cells and which are not cancer]. I had it checked out and it was a bit of a bomb shell to find it was cancer."

Just over two weeks after her cancer diagnosis, Sarah had a lumpectomy and her lymph nodes removed (to see whether the cancer had started to spread), followed by chemotherapy. Initially, her doctors did not mention fertility to her, and it was only after she researched breast cancer on the Internet and brought the subject up herself that it was discussed.

"The unspoken attitude is still very much 'Why are you worrying about your fertility when we are trying to save your life?'. It was just not considered an issue. I found it a bit patronising," said Sarah, who lives in London.

"I hit lucky with the consultant oncologist that I saw. He is heavily into research and he understood about young women and fertility. He tried to get me onto a trial to have epirubicin, but he also made a call to an ART [assisted reproduction technology] facility, where a woman saw me the same day in her lunch hour."

Frozen embryos

As a result, Sarah was able to have eggs retrieved from her ovaries in her next cycle and she started chemotherapy immediately afterwards. The eggs were fertilised with her husband's sperm via ICSI (intracytoplasmic sperm injection), creating seven embryos, which were frozen. In remission and approaching 40, Sarah and her husband John decided to try to start a family. The best three of the frozen embryos were implanted together, but unfortunately Sarah failed to become pregnant. At present she is not planning to use the remaining embryos, but psychologically it helps her to know that they are there if she changes her mind.

"I think I may be ovulating naturally now, and if I become pregnant naturally that would be wonderful."

She pointed out that young women of her age represent a very small proportion of breast cancer patients, but for them, fertility is likely to be a big issue. "I needed more information, up front, and breathing space. Unless a woman's cancer is going to kill her in the next two weeks, then give them time to think about it. There are lots of difficult issues to come to terms with."

> The unspoken attitude is still 'Why worry about fertility when we are trying to save your life?'

is that not only would they have liked to have the options for fertility discussed openly with them up front, but also that they needed more time to assimilate the information and make decisions. Gahan said: "The decision-making process at the beginning was too hurried, and it was the medical profession that was pushing it forward. I needed more time to come to terms with the diagnosis, more time to consider choices and more time to consider fertility issues."

Estimates suggest that one in a thousand people is a cancer survivor, due to increased prevalence of the disease and improved treatments. Surbone and Fosså believe this makes it imperative for physicians to take the time to discuss all available options with their patients and to consider fertility preservation as an integral part of patient care.

Vickie Maye, 29, who is in remission from Hodgkin's lymphoma and pregnant with her first child (see p. 48), sums it up: "Cancer is not a death sentence. You can live a full life, so why should you not be able to have a family?"

Sentinel node biopsy gets an excellent report

Janet Fricker

The latest study on use of the sentinel node biopsy has prompted calls for the procedure to be universally adopted. But can inexperienced teams be trusted to get it right?

A new study has shown that the sentinel node biopsy can be a highly reliable way of checking whether breast cancer has metastasised to lymph nodes. The procedure avoids routine removal of axillary lymph nodes in breast cancer patients by looking only at the first node that lymph from the cancerous tissue drains to – the 'sentinel node'.

The study, which was published in January in the *European Journal of Cancer* (vol 41, pp231-237), followed 953 women operated for breast cancer who did not undergo dissection of the axillary lymph nodes, after a biopsy revealed no metastases in the sentinel node. Patients were initially examined at four-monthly intervals for three years and then at six-monthly intervals, with axilla palpation and ultrasound when deemed necessary.

The results after a median follow-up of 38 months, showed a much lower rate of overt ipsilateral axillary metastasis than had been anticipated.

An earlier validation study published in the *Journal of the National Cancer Institute* in 1999 (vol 91, pp368-373), had found metastases in the dissected lymph nodes of 6% of women with negative sentinel node biopsy results. Based on these results, and assuming all positive nodes become clinically evident at a constant rate over 15 years, the investigators in the current study were expecting around 13 patients to develop ipsilateral metastases.

The results showed only three cases of overt ipsilateral axillary metastasis (0.3%) – much lower than the expected 13. In all three cases, the women received total axillary dissection and are presently alive and well. In addition, results show the five-year overall survival rate of the whole series was 98% and that 55 unfavourable events occurred, 37 of which related to the primary breast carcinoma.

"These patients are surviving well – their curability is very high and they have an excellent quality of life," says Umberto Veronesi, from the European Institute of Oncology, Milan, Italy, who was a pioneer of the technique and was the principal investigator of the study. He adds that local morbidity following the sentinel node biopsy was low, with three cases of local haematoma, five cases of seroma, seven of local infection and six of limited anaesthesia of the arm.

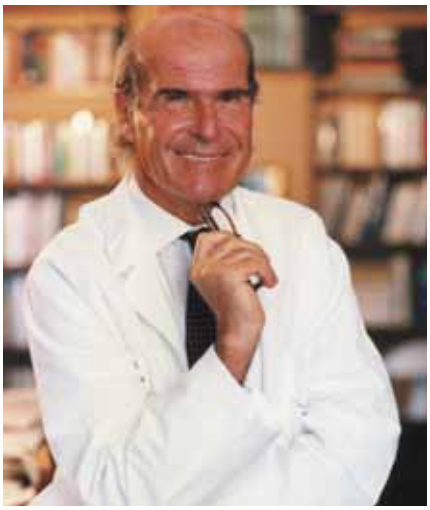
It is also noteworthy that only 20 women developed distant metastases – the trial team believe such low rates may be attributable to the beneficial effects of maintaining healthy immunological tissue.

The authors of the study believe their research confirms the safety of sentinel node biopsy and makes a strong case for its universal introduction. "After the results of this study I think all centres in the world should be undertaking sentinel node biopsy," says Veronesi.

This was the largest series yet following women with negative sentinel nodes, and it adds weight to earlier research by the same group, published two years ago in the *New England Journal of Medicine* (vol 349, pp546-553). That study showed the number of sentinel nodes identified with malignancies was the same for women who had undergone sentinel node biopsy followed by automatic axillary dissection as for those who only underwent axillary dissection if the sentinel node contained metastases. In the group randomised to receive automatic axillary dissection regardless of result, investigators found the overall accuracy of sentinel node biopsy compared to pathology of the other nodes was 96.9%.

Advantages

Veronesi's 2003 study had shown considerable advantages for sentinel node



Umberto Veronesi: Such low rates of false-negatives are widely accepted, given the advantage of avoiding axillary side effects

Emiel Rutgers: Results are from a single institution. You can't expect them to be replicated in centres with less experience

biopsy, with the women undergoing sentinel node biopsy experiencing less pain and better arm mobility than those who also underwent surgery. "Such low rates of false-negatives are widely accepted, since the advantage of avoiding axillary side effects is thought to outweigh any negative aspects," says Veronesi. He adds that removing normal lymph nodes in patients with cancer is now viewed as a biological mistake since it reduces their defence mechanisms.

Sentinel node biopsy is a simple procedure involving injecting 5–10 MBq of technetium-99-labelled human colloid particles in the sub dermis above the tumour or in the tissue immediately surrounding it. The sentinel node can be visualised 30 minutes to three hours later, with mammary and axillary planar scintigraphic scans, as it has the highest concentration of radioactive material.

Possible explanations for the lower than expected rate of ipsilateral axillary metastasis, say the investigators, include post-operative radiotherapy to the breast reaching the lymph nodes, and adjuvant treatment (mainly tamoxifen) delaying the clinical appearance of metastasis. But the most likely explanation, they suggest, is that a number of occult metastases will never become clinically evident, and will remain silent in a dormant state or may even disappear.

"Such thinking is in line with the new concept that in a population of cancer cells only a minority are stem cells with the ability to produce new cancer cells," explained Veronesi. "And if stem cells aren't present in the lymph glands the metastasis will disappear."

Exploring his theory further, Veronesi is conducting a new trial where women with positive sentinel nodes are being randomised to receive either axillary section or no treatment, with periodic PET (positron emission tomography) examination and ultrasound every six months. In the event of a metastasis appearing, the women would undergo immediate surgery. "We confidently expect the great majority of these women will not develop metastasis," he says, adding that ultimately they hope to identify a marker for stem cells that could be used to aid decision-making in sentinel node biopsy.

Emiel Rutgers, from the Netherlands Cancer Institute, comments that the results represent good news for sentinel node biopsy, but urges caution. "These results are from a single institution with extremely experienced surgeons, nuclear medicine doctors and pathologists. It's a best case scenario which can't be expected to translate to all centres," he says.

Indeed, a recent phase III trial involving about 140 centres, presented at the San Antonio meeting in December, produced a false-negative rate of 9.7%. In other words, in about one in ten patients lymph node metastases in the axilla were missed[1]. "To me this is difficult to accept. It's only fair that when women have this procedure they're informed of the risks they're taking for that institution," says Rutgers, adding that increasing the number of these procedures undertaken by individual surgeons has been shown to decrease their failure rate of identifying the sentinel node. "To be considered competent, breasts surgeons need to undertake at least six sentinel node procedures a month, but ideally it should be 10 or 20." Furthermore, he says, surgeons who offer this procedure to their patients need to work within an experienced 'SN-team', comprising an experienced breast surgeon, nuclear medicine specialist and pathologist.

1. Preliminary technical results of NSABP B-32, a randomised phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients.

Putting breast cancer on the political agenda

How Karin Jöns MEP is helping improve breast care across Europe

Mary Rice

Two years ago, the European Parliament passed a landmark resolution which set goals and standards for breast cancer services. It all started when a surgeon saved Karin Jöns MEP from an unnecessary mastectomy, and introduced her to the concept of specialist breast units. "This is what women need. You are a politician. Do something," he said. So she did.

Karin Jöns has been a member of the European Parliament since 1994. In June 1999, when she had just been re-elected, she was told that she had breast cancer. Her diagnosis and subsequent treatment have made her a tenacious advocate of the rights of European women with breast cancer to have the best possible diagnosis, treatment and care. For someone who by her own admission became interested in breast cancer "by accident", she has a remarkable record in attracting political support to the cause.

Jöns was born in Germany and brought up in Sweden. As an MEP she now works between three cities – Bremen, Brussels, and Strasbourg – and to add to the logistical problems, her husband also works abroad, currently in Tel Aviv. "He was in Warsaw when I was diagnosed," says Jöns, who is clearly used to relying on her own resources to get her through difficult times, though she adds "during this time, we managed to see each other more often. It's true that to meet we often have to undertake a top logistical performance, but it is always worth it!"

"At the time of my diagnosis – during a so-called routine mammography – my election posters were still up all over the region," she says. "Therefore I managed to get an appointment with four different specialists – today I would say 'so-called specialists' – on the same day. They all wanted to do surgery, without any further examination, in the next four days." But Jöns was unconvinced. She decided to ask around among friends and physicians, including some outside her region.

By the next day she had found the address of what was at the time the only hospital in Germany that specialised in breast cancer, which was a few hundred kilometres from where she lived.

"The treatment started eight days later. If I had decided to go ahead with surgery and treatment in my own region, I am convinced that I would have had a total mastectomy instead of breast-conserving surgery.

But even today many women do not have the chance to get quality treatment in a multi-disciplinary breast centre."

LEANNE FAIRLEY

MEPs hear about the importance of implementing breast screening in accordance with European guidelines at a meeting organised by the European Parliamentary Group on Breast Cancer and Europa Donna this January

Making policy

Jöns' greatest political achievement in the fight against breast cancer was the adoption of the resolution 'Breast Cancer in the European Union' by the European Parliament in 2003. It had to be introduced as an 'own-initiative report', through a lengthy process which Jöns says required both patience and perseverance. "It is difficult to get topics outside the general legislative process onto the agenda, however important they may be. Thus everyone who wants to introduce an own-initiative report has to point out very clearly to the different political groups why the topic is more important than others and needs to be discussed. This is even more difficult when the report targets an issue, such as breast cancer, where the European Union does not have any legislative competence."

The breast cancer resolution was the first disease-specific resolution to go through the European Parliament (since then, a resolution on multiple sclerosis has also been adopted). As rapporteur, Jöns had to overcome numerous obstacles. Even members of the Committee on Women's Rights thought the demands were too far-reaching. "I had to find countless forms of compromise without watering down the essential requirements for screening and treatment," she says. "In the end, though, I think we had an excellent resolution, acceptable to all, and finally adopted by the European Parliament with unanimity."

It is a great achievement, but has the resolution really made a difference on the ground? Jöns is less sure about this. "We really don't know at the moment. The resolution was only adopted two years ago and therefore Member States haven't had much time to implement it." One problem is that there is no central body able to monitor implementation and assess whether national governments are complying and increasing their efforts in the fight against breast cancer. However, Jöns is encouraged by the fact that after the resolution was adopted

by the Parliament, health ministers of the 15 states then in the EU (the EU-15) adopted a recommendation on cancer prevention that advises Member States to implement screening programmes for breast, cervical and colorectal cancer.

Jöns stresses that, with regard to bringing down mortality rates, the resolution called specifically for Member States to set themselves the target of creating the conditions required for a 25% reduction in deaths from breast cancer by 2008. "Things change slowly and I was realistic enough to ask for feasible changes within a realistic timeframe."

TRISTAN VANKANN

She also points out that many of the 10 states that joined the EU last year have very different baselines of cancer treatment to the EU-15, and have a long way to go before they can meet the targets set out in the resolution. But this makes fighting for improved breast cancer services in these countries all the more important. "I would like to encourage women in all Member States to impress on both physicians and politicians the need for more quality assurance in the early detection and treatment of breast cancer. Races for the cure and other charity events are important in awareness-raising, but even more important is the fight for structural changes in the entire care of breast cancer."

Another aim of the resolution was to reduce the disparities in five-year survival from 16% to 5% by 2008. There is little evidence to show that this is underway, but Jöns is optimistic. She cites as examples France, where the national screening programme has been completely revised, Germany, which has met the requirements to hopefully implement a countrywide screening programme by the end of this year, and Hungary, where she says huge progress has been made in screening.

She also points out that Member States are now debating the introduction of specialist breast units, and that, despite the current lack of clear EU guidelines for the certification of breast units, a great deal of progress has been made in setting up specialist units in national hospitals. "I have great hopes in the work of the European Breast Cancer Network, which is in the process of drafting the EU guidelines based on the 2000 requirements of EUSOMA [the European Society of Mastology], which will be published by the European Commission at the end of this year."

Changing practice

There is no doubt that, in order to improve survival rates, both quality-assured early detection and optimal treatment in multidisciplinary breast units are needed, says Jöns. However, this

"I had to find countless forms of compromise without watering down the essential requirements"

"Things change slowly and I was realistic enough to ask for feasible changes within a realistic timeframe"

returns once more to the question of compliance by Member States. You can have all the resolutions and good intentions in the world, but if no-one is chasing up those who are supposed to implement them, there probably won't be much change.

Jöns is well aware of this problem. "As Members of the European Parliament, we need to maintain strong relationships with our colleagues in national and regional parliaments. We must pass on to them information about progress made in other countries. And we should not forget to keep breast cancer on the agenda in the European Parliament."

She also hopes to convince the new European Commission to submit a mid-term review on the implementation of the resolution in 2006. This would provide essential information about what has been done across Europe, which could be used to identify best practice and provide reference points to measure progress across the EU – so-called 'benchmarking'. Jöns is grateful for the support she received from David Byrne, who was Health Commissioner until last May, and says she is very hopeful that the new Health Commissioner, Markos Kyprianou, will be as good an ally.

But perhaps the most important ally in ensuring that the aims of the breast cancer resolution become reality, says Jöns, is the patient advocacy movement. "Without Europa Donna we would not be where we are today in the fight against breast cancer. They provided excellent information from their national groups in the drafting of the resolution and they are now working consistently on the dissemination of the terms of the resolution in the old and new Member States." As rapporteur on breast cancer, she says she received support from a range of advocacy groups, and she is confident that this sort of Europe-wide collaboration will continue to influence practice at both European and national level.

Personal and political

Jöns acknowledges that, had she not had breast cancer herself, this subject might not be so high on her political agenda. Having had her surgery in a multidisciplinary unit, it was her surgeon who first introduced her to the EUSOMA requirements for breast units. "He gave me a copy of the first draft and said: 'This is what women need. You are a politician. Do something.'"

In the beginning, she says, it wasn't easy. She started by working with Europa Donna to build support for a cross-party European Parliamentary Group on breast cancer, which has been key to the subsequent work. The Group also acts as a forum where there is a constant exchange of information and opinions on breast cancer issues. The topic for its next meeting is the use of structural funds for the implementation of mammography screening. This, says Jöns, is one of the most important questions in healthcare reform and setting up new programmes, especially in new Member States.

It all bodes well for the future of breast cancer treatment in Europe, but does Jöns ever feel the need to get involved in some of the less 'fashionable' cancers, such as lung, prostate, or colon, which receive far less media coverage and where patients seem more reluctant – or less able – to speak out?

"It is true," says Jöns, "that breast cancer is high on the political agenda, but this has been achieved by women themselves, united in Europa Donna or other initiatives that have been working hard to raise public awareness of the disease. In the EU-25, a woman is diagnosed with breast cancer every six minutes. Every two minutes a woman dies from this disease. We ourselves have gathered together and organised, and learnt more about the fight against breast cancer. Men can do this too!"

She admits that women may find it easier to speak more openly about breast cancer than

LEANNE FAIRLEY

In conversation with Lawrence von Karsa *(left)*, coordinator of the European Breast Cancer Network, and Karl Freese, Policy Officer at the European Commission directorate general for Health and Consumer Protection

men would about prostate cancer, for example, but says: "This difference is not God given. If men know how to talk about the stock market, for example, why cannot they speak about cancer?" She also argues that there are still not enough women in politics and society who are prepared to say that they are breast cancer patients or survivors. "This is one area where we can learn a lot from the USA."

Jöns refutes the suggestion that other cancers have been forgotten at European level. She points out that screening for cervical and colorectal cancers is included in the EC recommendations on cancer prevention, and that the framework research programme includes funding for projects in prostate cancer and leukaemia. She also mentions a new European campaign against tobacco, which will help fight the increase in lung cancer.

As for breast cancer, despite the successes, Jöns argues that there is still a great deal left to do. She is looking forward to the publication of the fourth edition of the European guidelines on mammography screening, which will include, for the first time, guidelines for digital screening, and will have integrated evidence-based requirements for breast units and criteria for their accreditation. "To have these documents at hand will be a big step forward for quality assurance in breast cancer."

She is also looking towards a second resolution on breast cancer, once data on the implementation of the original resolution become available.

Looking back on it, rarely can the exhortation "Do something!" have been met with a more committed and effective response. And hundreds of thousands of women in Europe have cause to be thankful that Jöns not only did something, but looks set to continue fighting their corner on breast cancer services for many years to come.

"We ourselves have got together and learnt to fight against breast cancer. Men can do this too!"

Science
or humanism?

➜ Raphaël Brenner

Two new oncological publications offer equal value in terms of their scientific and medical content. Where they differ is in their approach to patients and in their human vision.

Two clinical oncology books have recently hit the market: *Clinical oncology*, a blockbuster textbook of more than 3000 pages, and the more modestly sized *Manual of clinical oncology*. The first of these, edited by Abeloff et al, is a heavyweight work very similar in form to its main rival *Cancer: Principles and practice of oncology* (De Vita et al., reviewed in the last issue of *Cancer World*). *Clinical oncology* is divided into three main parts. Part one presents the basic science of oncology, part two addresses problems relating to cancer and cancer therapy, and part three is devoted to each specific malignancy, including childhood cancers.

The book offers an impressive array of information on science and clinical medicine, including an in-depth chapter on alternative medicine, and readers will find it a mine of information on almost every issue pertaining to the biological and somatic aspects of cancer. But, while the authors stress the importance of a multimodal approach to cancer therapy, they almost completely ignore the psychological aspects and their book suffers from the same misconception as DeVita's – namely that the disease, rather than the patient, is the heart of the matter. There is barely a trace of the 'humanism' of which the editors boast in their preface. The strong point of the Abeloff textbook, compared to DeVita, is its generous four-colour design and user-friendly layout. Its weak point is the lack of detail in the table of contents and the limitations of the accompanying CD-ROM, which only contains illustrations featured in the book.

The second of the two books, the *Manual of clinical oncology*, is edited by Casciato et al. Oncology fellows, residents and general physicians searching for a handy, concise, up-to-date, comprehensive textbook on oncology will greatly appreciate this work. Although similar in structure to Abeloff, here, specific malignancies are advantageously addressed in a uniform format, and attention is given to providing information useful for making diagnostic and therapeutic decisions at the bedside of cancer patients. What makes this thoroughly updated 5th edition really different from other oncology manuals is the human vision it conveys and the central role it affords to patients. The aim of the *Manual*, writes Casciato, is to "provide the caregiver with the ability to temper today's popular interventions with good judgment and cautious open-mindedness to the promise of tomorrow." In contrast to the more heavyweight oncology textbooks, Casciato succeeds in fusing together the technical, clinical and human approaches in oncology. The book has a soul, and it owes much to Barry B. Lowitz, co-editor of the first four editions, whose humanism is felt throughout the book, as in the wonderful chapter "Talking with Cancer Patients and their Families." His witty remarks are also a plus. Here is a typical gem: "Avoid the cutting edge of oncology because it slices up too many people."

Clinical oncology: *3rd edition*
Edited by Martin D. Abeloff, James O. Armitage, John E. Niederhuber, Michael B. Kastan and W. Gillies McKenna
Churchill Livingstone/Elsevier, 3232 pp, £195.00

Manual of clinical oncology: *5th edition*
Edited by Dennis A. Casciato
Lippincott Williams & Wilkins, 778 pp, $44.95

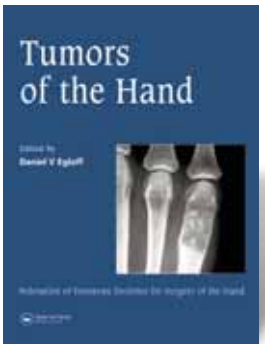
Tumors of the hand

Edited by Daniel V. Egloff
Taylor & Francis, published in association with the European Societies for Surgery of the Hand
224 pp, £75.00

Management of tumours of the hand, wrist and peripheral nerves requires a multidisciplinary team of pathologists, oncologists, radiotherapists and hand surgeons. This detailed and richly illustrated book is aimed at orthopaedic surgeons and oncologists versed in this field. It provides coverage of all the main issues of concern, from the anatomical to the oncological and surgical – both ablative and reconstructive.

The book also presents data of statistical value amassed by some of the leading researchers and institutions in the field. Written by European specialists, it covers almost the entire domain of hand tumours, benign and malignant. The latter include not only squamous cell tumours, but also less common tumours including basal cell tumours, rare melanomas, chondrosarcomas and osteosarcomas. An entire chapter is also devoted to metastatic tumours of the hand and wrist.

Fortunately, tumours of the hand tend to be identified relatively early, since they are more noticeable than other tumours, and the prognosis is therefore generally more positive.



Atlas of clinical hematology

3rd edition
H. Löffler, J. Rastetter and T. Haferlach
Springer, 444 pp, euro 199.95

With over 1000 illustrations, mostly in colour, the 6th revised edition of the *Atlas of clinical hematology*, which was first published fifty years ago, covers the whole spectrum of haematology. This includes all the microscopic methods in haematology which form the basis of diagnosis, as well as the modern immunologic, cytogenetic and molecular-genetic characterisation of the various haematologic diseases. Two thirds of the book is devoted to haematopoietic malignancies. The 2001 WHO classification of pathology and genetics of the haematopoietic and lymphatic tissues has been integrated in the *Atlas*, which also covers new types of leukaemia and lymphoma-type leukaemias of dendritic cells, intravascular large B-cell lymphoma and liver-spleen T-cell lymphoma. Normal results and pathological findings are compared, and the various findings made during therapy are depicted.

The quality of the illustrations and the clarity of the accompanying texts make the *Atlas* a valuable companion to the haematology and oncology professions.

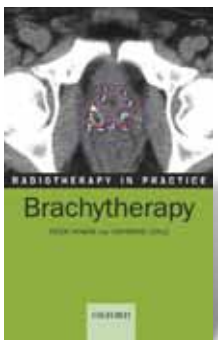
Radiotherapy in practice: Brachytherapy

Edited by Peter Hoskin and Catherine Coyle, Oxford University Press, 213 pp, £29.95

For non-specialists, and even more for patients, brachytherapy – derived from the Greek root brachus (short) – sounds barbaric and threatening. It consists in the delivery of radiation therapy at short range, using capsules or other sealed sources that are placed as close as possible to the site being treated.

Written by leading British experts in this field, this small book manages to make brachytherapy understandable to physicians and other professionals. The short, clear chapters, full of helpful illustrations, provide readers with the scientific fundamentals in the physics and dosimetry of the technique, and with practical guidelines on its use in common disease sites.

The book covers low-, medium- and high-dose-rate techniques, but the main emphasis is on high-dose-rate afterloading techniques, which allow the radioactive material to be inserted after the capsule has been placed. In combination with external beam radiotherapy, brachytherapy allows higher doses to be used with less damage to surrounding organs compared to external beam techniques.



Cancer pain: assessment and management
Edited by Eduardo D. Bruera and Russell K. Portenoy
Cambridge University Press, 500 pp, £130.00

The last 15 years have seen major advances in our ability to control pain. Oral morphine has become the mainstay of therapy for serious cancer pain therapy, at least in the Western world, and specialists now agree that pain can be relieved in 70%–90% of cancer patients. Yet an increasing body of evidence shows that cancer pain is often poorly assessed and undertreated.

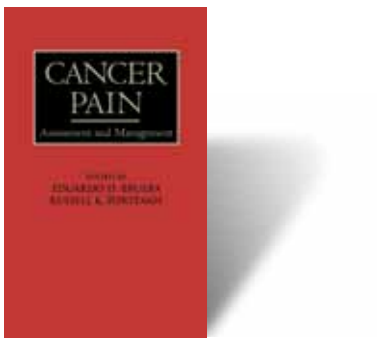
According to the editors of *Cancer pain*, the main reason for this lies in inadequate healthcare and poor professional education, which result in prejudice and a failure to actively listen on the part of many healthcare professionals, particularly physicians.

Written by an international team of contributors, *Cancer pain* provides a truly comprehensive, clinically oriented, scholarly review of all aspects of this complex, multidimensional issue, including the ethical foundations of pain in medical illness and the particular way pain manifests itself in specific populations such as the elderly and children.

The textbook argues that management of pain is most effective when it is included as part of an integrated treatment plan, devised and implemented by an interdisciplinary team that includes family caregivers, and it contains a very helpful chapter that looks at the role of family caregivers in cancer pain management.

It also discusses the unique characteristics of cancer pain – its pathophysiology, epidemiology, clinical assessment, diagnosis and pharmacological and non-pharmacological management. Of note, among the latter, are chapters on psychological interventions and rehabilitation medicine interventions (ambulatory aids, massages, acupuncture, prayer, etc.).

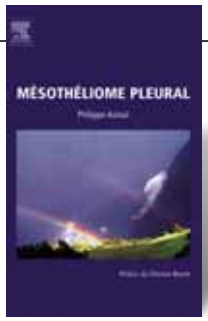
While rehabilitation disciplines have much to offer cancer patients in pain, observes Theresa Gillis, "access to rehabilitation disciplines is frequently limited by knowledge gaps among oncologists, patients and rehabilitationists themselves." The book is a helpful resource for all those dealing with cancer pain – physicians, nurses and medical students alike.



Le cancer du poumon
Edited by Jean Trédaniel
Masson, 334 pp, euro 60.00

Mésothéliome pleural
Edited by Philippe Astoul
Elsevier, 238 pp, euro 30.00

Two French publications give a complete and up-to-date picture of lung cancer and pleural mesothelioma. The management of lung cancer has seen two major advances in the last decade. One is the use of integrated positron emission tomography (PET) scan and computed tomography, which has dramatically changed diagnostic evaluation, particularly in the detection of metastases. The other is chemotherapy, which has been shown to be effective and is now being used in conjunction with surgery and radiotherapy.



Despite these advances, lung cancer remains the number one killer among cancers in most of the Western world, and the majority of lung cancer patients are still being diagnosed at a late stage in the illness (IIIB or IV). The culprit is, alas, well known and Trédaniel rightly devotes two lengthy chapters to epidemiology and prevention.

Astoul's book, the first in French on malignant pleural mesothelioma, is of an equally high standard. Although the incidence of mesothelioma is low, it has steadily increased in France over the last two decades and is expected to rise significantly over the next two. Though the risk of the disease from asbestos exposure was acknowledged in 1960, thousands of workers have continued to be exposed to this killer material. Due to the long latency of the disease (30–40 years), these workers are expected to develop malignant mesothelioma in the near future, in what Astoul terms "a tremendous failure of preventive medicine."

European research crisis: the cancer community must make its voice heard

Anna Wagstaff

The European Union aims to become "the most competitive and dynamic knowledge-based economy in the world". Why then does it put so many obstacles in the way of research? And why is a world-beating breast cancer trial left short of funding and support?

A clinical trial of breast cancer treatment in Europe is about to set new standards for the future of research by focusing on the molecular biology of tumours, rather than simply asking whether one treatment is better than another.

This is the first large trial anywhere in the world to put to the test the best system for choosing which tumours respond best to which treatment. It could put Europe in the forefront of the drive to target treatments to the genetic fingerprint of individual breast cancers.

But this revolutionary approach is being held back by a culture of bureaucracy, lack of coordination and lack of funding which threatens Europe-wide research. The European Commission says it has learned lessons from an avalanche of criticism. It may have one last chance to put money where it is needed and to remove barriers that hold back Europe's scientists and clinicians, before cutting edge research moves decisively to the USA or to .China and other parts of Asia.

The world's first trial of tailored treatments, MINDACT, is being masterminded by TRANSBIG – the translational research arm of the Breast International Group – from a small office in the Jules Bordet Institute in Brussels. It will analyse the molecular biology of every tumour in the trial, to gain information on which types of tumour respond best to which types of treatment.

MINDACT (MIcroarray for Node negative Disease may Avoid ChemoTherapy) aims to find out whether the genetic signature (gene expression profile) of an early-stage breast cancer tumour is more effective than traditional clinical and pathological criteria at predicting which women will benefit from adjuvant chemotherapy following surgery. The ultimate aim is to avoid giving chemotherapy to women who do not need it – to the benefit of both patients and health care budgets.

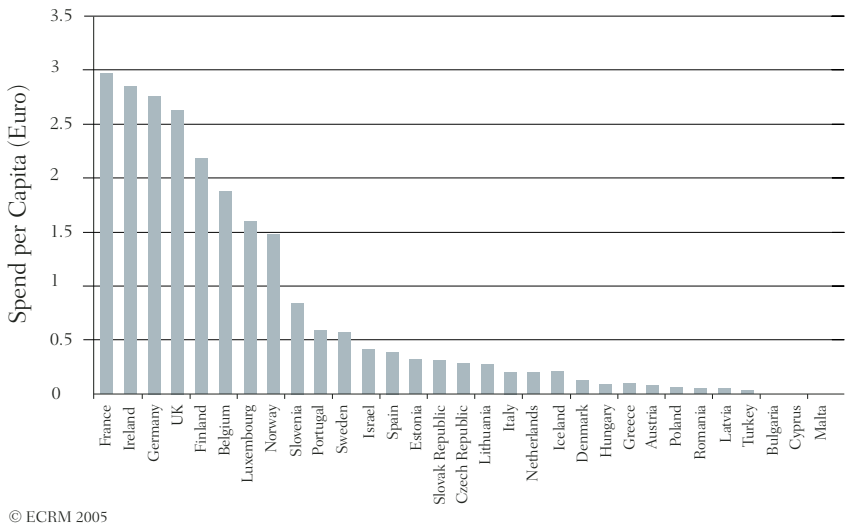
It is a huge logistical challenge that requires lab-based specialists in genomics, proteomics and bioinformatics in a number of centres around Europe to work in harmony with hospital-based clinicians – medical oncologists, surgeons, pathologists and nurses.

More than 6,000 patients will be recruited and enrolled by more than two hundred centres in Europe, Latin America, and in other countries around the world. Clinicians will use current clinical and pathological criteria to categorise each patient as high or low risk.

Tumour tissue will be sent to Milan for pathology quality control.

Philippe Busquin, former Commissioner for Research, was a leading force behind the 2000 'Lisbon agenda', which aimed to turn the EU into the world's leading knowledge-based economy. But his recent book, *The Decline of the European Scientific Empire*, strikes a pessimistic note

TABLE 1. GOVERNMENT FUNDING OF CANCER RESEARCH



Two-thirds of European countries spend less than 1 euro per head on cancer research each year

Source: European Cancer Research Funding Survey, European Cancer Research Managers Forum, 2005. The data are for the years 2002-2003. A full copy of the report can be downloaded from *www.ecrmforum.org*

Meanwhile, frozen tumour tissue samples will be sent to the Netherlands Cancer Institute (NKI) in Amsterdam, where genomics specialists will work with the microarray company Agendia to categorise them as high risk or low risk according to a prognostic gene expression pattern – known as the '70-gene signature' or MamaPrint – which was developed in Amsterdam.

Patients categorised as high risk by both methods will be treated with chemotherapy, and those categorised as low risk by both will be treated with hormonal therapy (so long as their tumours express hormone receptors). Those categorised as high risk by one method and low risk by the other will randomly have their treatment decided either by clinical-pathological criteria or by genetic signature. The hypothesis being tested is that the genomic signature will prove a more accurate marker of risk, and so reduce unnecessary chemotherapy.

Meanwhile, tumour and blood samples from every patient will be flown to a proteomics lab in Wales, where specialists will analyse their protein profiles, to try to identify "protein signatures" associated with risk, or with responses to particular therapies. Many scientists believe that proteins will ultimately prove more useful than genes in distinguishing cancers, and this method requires only blood rather than frozen tissue.

One of the main aims of TRANSBIG is to develop user-friendly tools for risk assessment and to predict response. To this end, molecular biologists will use polymeric chain reaction (PCR) and other widely used techniques to determine whether the genetic profile of the tumour can be evaluated using these less expensive and less demanding methods. Validation of such straightforward techniques will be essential if cancer treatment centres are to be able to act on the outcome of the trial.

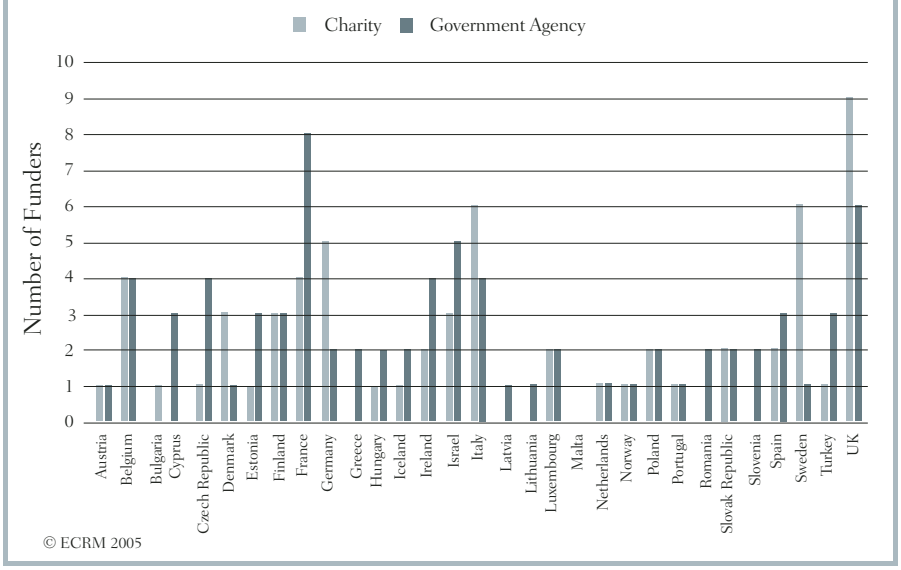
To add to the complexity, two additional questions are posed in this trial. Patients treated with chemotherapy will receive either anthracycline or taxane plus capecitabine, with the aim of comparing their efficacy and serious side-effects. Patients treated with hormonal therapy will receive either 2 years tamoxifen plus 5 years aromatase inhibitor, or 7 years aromatase inhibitor.

As far as the scientists are concerned, these are tag-on questions, but revealingly, their inclusion will finance much of the trial. Pharmaceutical companies have no great interest in differentiating high-risk from low-risk patients, but finding markers that predict which patients respond best to their products is of value to them, so the chemotherapy and hormone therapy questions tie in their support.

MINDACT is a magnificent trial opening up new frontiers in the prized and fast-expanding field of 'omics' biotechnology. It will take a sizable step towards true individualised treatment in the future based on the 'fingerprint' of a woman's tumour. It should be the pride and joy of the European Union (EU) which, at a landmark conference in Lisbon five years ago, committed itself to becoming "the most competitive and dynamic knowledge-based economy in the world by 2010".

The sad reality, however, is that MINDACT, like most European research, receives far too little funding, relies on clinicians doing research in their 'spare time', struggles with the heaviest clinical trials regulation in the world, and depends on a continually depleted pool of European scientific expertise as researchers are attracted by funding and career prospects in the US.

TABLE 2. DISTRIBUTION OF FUNDING ORGANISATIONS BY COUNTRY



Half of all European cancer research funding comes from charities. This reflects very poorly on government funding – it also highlights the importance of involving cancer charities in strategic planning at national and European levels

THE DECLINE OF EUROPEAN RESEARCH

Europe's record on supporting research and researchers leaves a lot to be desired. Some 400,000 European scientists are currently working in the US, and a survey published last year by the Commission indicated that only 13% are currently intending to return home. While 15 years ago the pharmaceutical industry invested 50% more in the Europe than in the US, today it is investing 40% more in the US than in Europe, and Europe's base of expertise in drug development has suffered as a consequence. Today, the US itself fears being overtaken by the fast growing economies of China and South Asia, which are investing heavily in biotechnology. For the first time, the number of scientists from these regions returning home from jobs in the US is outstripping the number flowing the other way. American analysts predict a serious shortfall in scientific personnel – and this will exert a further pull on Europe's postgraduates.

No wonder former Commissioner for Research, Philippe Busquin is sounding the alarm. His book, *The Decline of the European Scientific Empire*, charts the path of European science from after the Second World War to the present day. He issues a rallying cry for European leaders to support the vision of a knowledge-led economy set out in Lisbon in 2000, and to fulfil their pledge to increase funding for research and development to 3% of gross domestic product (GDP).

THE FUNDING GAP

The cancer research community has been complaining about the shortfall in European research funding for many years. The European Cancer Research Managers (ECRM) Forum – a body supported by the EU – commissioned a study into non-commercial funding of cancer research in Europe, which published its results at the end of March 2005. Even they were shocked at what they found.

Europe spends 2.56 euros per head on cancer research – one seventh of the 17.63 euros per head spent in the US (see Table 1). If the ten countries that joined last year are excluded, the figure rises slightly, to one-fifth of the US per capita spend. Moreover, government agencies account for only half of the total European spend of 1.43 billion euros, the rest coming from charities. In other words, Europe's cancer research relies on philanthropy (see Table 2).

Funding of cancer research via EU research grants came to 90 million euros. This was sufficient to finance only one in five fundable projects, and only 50% of the projects judged to be of a very high standard.

No country comes out of the survey well, but there are some real surprises. At 6.43 euros per head, Sweden ranks second after the UK in per capita spend on cancer research, but only 0.56 euros of this comes from the government, with more than 90% being contributed by Swedish cancer charities. The Swedish government contribution is only 0.002% of GDP. This compares with 0.0078% in Slovenia, 0.0063% in the Slovak Republic, 0.0063% in Estonia, and 0.0042% in Lithuania – all poorer countries that could be expected to concentrate more heavily on service provision rather than research.

Sweden is by no means the worst. Out of 31 countries in the European Free Trade Area, it ranks 17th on cancer research spend as a proportion of GDP – ahead of Italy, the Netherlands and Iceland, (23rd to 25th). In Denmark and Austria, ranked 27th and 28th, the governments spend a

shameful 0.0003% of GDP on cancer research – around one fortieth of the proportion spent by France, Germany and the UK.

This goes some way to explaining why even flagship research projects such as the MINDACT trial, which uses precisely the cutting-edge techniques and technologies the EU says it will invest in, is finding it hard to get sufficient funding.

This technology doesn't come cheap and MINDACT will cost around 30 million euros. Although the EU Research Framework Programme promises support for "clinical research aimed at validating interventions", its support for the MINDACT trial is only indirect. TRANSBIG has been given 7 million euro under the EU Networks of Excellence Programme, to be spent largely on the network's "integrating activities" related to MINDACT. None of this money will go towards the costs of the actual clinical trial or microarray studies.

TRANSBIG is urging national governments and health insurers to contribute towards the costs, following the lead of the Dutch medical health insurers who helped finance some of the clinical research with the 70-gene signature. So far, however, not one government or health insurer has pledged any funds.

Fatima Cardoso, TRANSBIG's scientific coordinator, is baffled at the lack of support. "You would think that a trial like MINDACT, which has the potential of telling you that we can reduce the number of chemotherapy prescriptions by 10–20%, would be of extreme interest to governments, health insurance companies and the Commission," she said.

Clinical trials – the poor relation

One of the six key messages from the ECRM survey is that the funding shortage is "seriously damaging" clinical research.

The gap between US and European funding for clinical cancer research is even greater than that for basic research. One reason is that most clinical trials need to be conducted at an international level to recruit enough patients, yet national charities and government research funds rarely contribute to the international initiatives. One key recommendation from the survey is for greater coordination between major non-commercial funding bodies at European level.

Another reason is the EU refuses to help fund clinical trials, despite the fact that most cannot be undertaken by a national group acting alone. Françoise Meunier, Director General of the European Organisation for Research and Treatment of Cancer (EORTC), which is running the clinical arm of MINDACT and is responsible for the vast majority of clinical trials in Europe, is exasperated at this lack of support. She has spent years trying to convince the Commission to accept a responsibility for helping to fund non-commercial clinical research.

The Commission says that this research is too expensive for public funding and should be financed by cancer charities, national governments and the pharmaceutical companies. The net result is that clinical research – which has the greatest immediate impact on patient care – is left largely in the hands of the industry. However, as Meunier has tried to explain, many clinical trials are of no interest to the pharmaceutical industry.

Pharmaceutical companies focus their attention on the four most prevalent cancers – breast, lung, prostate and colorectal. There are regulatory incentives to encourage companies to research treatments for 'rare diseases', but most cancers do not qualify as rare. Meunier points out that breakthrough drugs like temozolamide for glioblastoma or novel indications such as imatinib (Glivec) for use in gastro-intestinal stromal tumour (GIST) came out of academic research.

Child cancers is another neglected area. Companies may soon have to provide data on the use of their drugs in paediatric populations, where appropriate, as a condition of getting approval. However, as children rarely suffer from the cancers that are common in adults, this is unlikely to be of great use. Conversely, the vast majority of children's cancers are rarely found in adults; the question is who will fund research into these diseases?

Some clinical trials do not concern drugs at all. Many important benefits have resulted from refining radiotherapy techniques, improving surgical procedures, and finding more effective ways to combine radiotherapy, surgery and drug treatment. If only drug trials were funded, women would still rou-

Doctors and nurses who want to participate in research usually have to do it in their spare time

THE CLINICAL TRIALS DIRECTIVE

Europe's spectacular own goal

In May 2003, the EU adopted a directive governing the way clinical trials are conducted. Clinical researchers hoped this might boost trans-European clinical research by harmonising national regulations governing insurance requirements, ethical approval, reporting requirements and so on. It didn't.

Not only did the Clinical Trials Directive leave the original obstacles in place, but it added new ones. Each trial is now obliged to have a 'sponsoring' research body or institution. Among a raft of bureaucratic, financial and legal obligations, the sponsors will be required to pay for every drug used by every patient enrolled in the trial, and to meet the costs of any inspections. The requirements of data validation and reporting go well beyond anything that regulatory bodies demand when assessing a new drug for approval, and in many cases the researchers find themselves having to report the same data in two different ways in order to satisfy both EU and national requirements.

The Directive was drawn up by the directorate general for Enterprise as a 'single-market measure'. It aimed to provide a level playing field for the free movement of medicines in the EU, and therefore included regulations on how the pharmaceutical industry conducts its research on patients. But it ended up dragging down non-commercial research in the same net.

Europe's research community warned at the time that the Directive could threaten the future of non-commercial clinical trials. They have been proved right. At the end of April, almost exactly one year after the directive came into force, the EORTC, Cancer Research UK and other bodies involved in clinical research sat down with the Commission and representatives of the member states to report on the damage. They were able to show that all over Europe non-commercial trials activity has been reduced by 50% while the costs and the administrative burden have doubled. The new requirement for sponsorship has stopped many national clinical trial groups from opening any centres in other EU countries. Though the point has been proved, the Directive will stand unless Europe's cancer researchers mount concerted pressure to force the EU to rethink its whole approach.

tinely lose their breasts and throat cancer patients their voice boxes.

Lack of funding means that the EORTC has to be highly selective, and as a result many urgent questions regarding treatment options are simply not investigated. This situation is exacerbated by the extra costs associated with the EU Clinical Trials Directive, which came into force in May 2004 (see box).

Missing the drugs train

Silvia Marsoni, head of the Milan-based Southern Europe New Drug Organisation (SENDO), says that lack of investment is also crippling the EU's ability to compete in the potentially lucrative drug development market. Advances in molecular biology offer the promise of effective treatments for many diseases and even have the potential to alter natural physiological processes such as ageing. Economically, this represents a goldmine. "The US, China, India and Korea are all pouring money into this field," says Marsoni. "The EU risks missing the train."

Europe lost much of its pharmaceutical industry to the US in takeovers and mergers in the 1980s and '90s. However, a lot of innovative work is now coming from smaller science-driven biotechnology companies, and the EU is pinning its hopes on this sector.

Marsoni says that some countries, such as the UK, France and Sweden, are trying to create an environment to ease the route from scientific discovery to marketable product. But in much of Europe, this is not the case. "The concept of venture capital does not exist in Italy. You cannot get a loan unless you have a house to give as security."

But even a thriving European biotech sector will not develop drugs and take them to market without scientific expertise in many different areas.

SENDO is one of very few non-commercial bodies to offer drug development services in Europe, along with Cancer Research UK and the EORTC. It struggles to maintain a base of drug development expertise in Europe, without which the biotech companies will have to look elsewhere.

Marsoni says, "It's a niche area. You need very skilled people, and you need to invest in them. It takes me five years to train up good people. Unless I have money to pay for their training, it's not going to happen." In addition, the Clinical Trials Directive has made research so much more bureaucratic that SENDO had to hire three extra people just to deal with the paperwork.

If the EU is to avoid being left behind, it will need to simplify its bureaucracy and start investing in infrastructure and research personnel – from clinicians to scientists and data managers.

Marsoni says that Europe has a short period of breathing space, because the rush to develop Glivec-style treatments aimed at a single tar-

Scientific innovation is not amenable to the top-down approach

get turned out to be a blind alley – but the next decisions have to be the right ones. "Five years ago, when the public understood the potential of molecular biology, we thought that with the genome we were on our way to solving the problem. Now we know we are dealing with pathways and networks. We are in a period of reflection. Either we understand what we have to do and we do it within 2005–2006, or we will definitely miss the train."

Losing the Lisbon plot

The Lisbon conference, which set the goal for Europe to lead the world in a knowledge-based economy, set out a strategy to build a European Research Area and Networks of Excellence in priority areas. These were spelt out in the Sixth Framework Programme (FP6) drawn up by the Commission's Directorate General for Research, covering the period 2002–2006.

FP6 was given twice the budget of its predecessor. "Life sciences, genomics and biotechnology for health" is one of seven major themes, within which support is concentrated on advanced genomics and applications for health and combating major disease.

The priorities are a cancer researcher's dream. Basic research includes gene expression and proteomics, structural genomics, bioinformatics, multidisciplinary approaches in functional genomics and fundamental biological processes and the application of knowledge and technologies in the use of biotechnology for heath. It also includes the development of patient-oriented strategies for diagnosis and treatment, translational research and clinical research aimed at validating interventions.

Some researchers argue that it not only reads like a dream, but is just as insubstantial. While a number of basic science projects have benefited from FP6 funding, scientists complain that funding instruments define research topics too narrowly, force people into unhappy partnerships, involve small businesses where they don't belong, and create an administrative nightmare.

To top it all, the EORTC itself is disqualified from receiving support even as a Network of Excellence, because only new networks are eligible for support. The same rule was applied to disqualify the Breast International Group (BIG), which receives no support from governments or the EU. TRANSBIG was created as a new consortium to get around this requirement.

You will study X

The Commission allocates most research grants after putting out calls for proposals on topics specified within the Framework Agreement. It has justified this approach by referring to the need to build a "critical mass" in priority areas.

Richard Sullivan, director of Clinical Research at Cancer Research UK, Europe's largest cancer research organisation, says that scientific innovation is not amenable to this top down approach.

"The whole point about innovation and pushing back the frontiers of science is that you can't predict in which direction it is going to go. Programme grants need to be very flexible and cover broad domains, and they need to be driven from the bottom up."

Defining research topics narrowly is a particular problem because bureaucratic organisations like the Commission are slow to respond to events. "You need to be able to react very quickly when somebody says, 'this is hot, it needs to be done in the next few months and it will revolutionise this area of work.' You are always guessing the future."

You will collaborate with Y

Researchers responding to a call are obliged to form a consortium to meet strict guidelines about involving a number of countries, particularly those with a poorer research base.

The theory is that the EU can make the value of research in Member States greater than the sum of its parts through promoting collaboration and minimising fragmentation and duplication of research.

But here too, Sullivan argues, the EU has got it wrong. "There is little evidence to show European cancer research is fragmented."

Indeed, while the ECRM survey identified 138 major funders of cancer research in Europe, more than 80% of that funding came from only 25 organisations. What is needed says Sullivan is more communication and collaboration between these bodies to support transnational research.

European cancer also has a highly developed system of international cooperative groups – lymphoma groups, breast groups, groups for paediatric oncologists, groups for radiotherapists. European clinical researchers have worked together in EORTC for decades.

Sullivan says, "Everybody knows who everybody else is. You know who your competitors are. You are either cooperating with them because it is mutually beneficial, or you are in ruthless competition with them, because you are working in the same area."

He says that forcing people to collaborate as a condition of funding is counterproductive since true scientific collaboration cannot be imposed.

One scientist, who had benefited from an FP6 Network grant, put it this way: "We collaborate with who we want to collaborate with, and we don't collaborate with who we don't want to collaborate with." He said that the rules create sham partnerships where partners do not really work with one another. "It's just a way of getting the money."

You will involve the private sector

Another irritation has been the frequent requirement to include at least one small or medium enterprise (SME). The rationale is to speed up the translation of research into marketable results, by narrowing the gap between scientists and private enterprise.

However, the questions that academic researchers want answered do not always coincide with the priorities of profit-driven companies.

The experience of TRANSBIG is revealing. Despite reservations, they agreed to include Agendia, the company that developed the microarray platform used in Amsterdam to generate the '70-gene signature', within the consortium. Meanwhile, a group in Rotterdam conducted a similar study using a different company and a different platform. Their study identified a 76-gene signature, which seems equally effective at differentiating tumours, but has only three genes in common with its Amsterdam rival.

Naturally TRANSBIG scientists are eager to compare the Rotterdam and Amsterdam platforms and signatures. Equally naturally, Agendia would prefer their platform to be the only one validated. As part of the consortium, Agendia has a say in how MINDACT proceeds. The trial steering committee think they have found a way to resolve the problem, but they are strongly urging the Commission to drop the requirement to include SMEs in future.

Red tape

The biggest complaint is about red tape. To comply with EU requirements, consortia are required to fill in a level of paperwork before, during and after a project that beggars belief, and is entirely inappropriate for academics and small businesses that have no civil service and very little administrative support.

After applying for his first EU grant, Steve West, a leading scientist studying DNA repair mechanisms, says, "never again". Sitting on his desk is the completed application – a pile of paper 10-cm thick. West estimates that only 20 pages of this are relevant to the science.

Although the grant is large, it has to be spread across 15 labs. When he compares this with the nine- or ten-page research proposals required by other bodies, West concludes that it is not worth the hassle.

He is not alone. In a consultation on the future of European research carried out by the Commission in 2004, the anger and frustration at red tape was identified as the "single most recurrent message of the consultation".

Lisbon relaunched

There are encouraging signs that the Commission is trying to take on board many of these complaints. Publishing its proposals for FP7 in April, it said, "The expansion of the scope, span and volume of EU action in research requires, as a condition sine qua non, a substantial simplification and rationalisation of the way the Framework Programme Works."

It talks of "reducing the burden of administrative and financial rules and procedures," judging value on results rather than by controls, and says that their general approach "will be one of trust towards the researchers." Recognising that projects have been too tightly defined, it talks of "focusing more on themes than on instruments" and promises sufficient flexibility to accommodate emerging topics. It even talks about "investigator-driven research", and proposes the creation of a European Research Council, led by leading members of

Consortia are required to fill in a level of paperwork that beggars belief

Some governments may cut their domestic research budget to offset higher contributions to the EU

the scientific community, which would control 15% of the research budget.

"The new 7th Framework Programme," says the Commission in a tacit admission of the level of disillusionment, "will not be 'just another Framework Programme'. In its content, organisation, implementation modes and management tools, it is designed as a key contribution to the re-launched Lisbon strategy."

To support this, the Commission proposes doubling the FP7 budget to 67.8 billion euros over a longer timeframe of seven years. It predicts that this will lever 93 eurocents of private investment in research and development for each extra 1 euro of public funding, which "will boost business confidence that Europe delivers on its commitments and offers an attractive future."

It is easy to be sceptical. But it would be churlish not to recognise the real effort the Commission is making to move European research up a gear, and members of the cancer research community now need to ensure that their own governments back this effort with political support and hard cash.

Over the next two years, the FP7 proposals will be debated by the European Parliament and in the Council of Ministers. This is where the cancer research community has a chance to lobby for improvements – for instance to allow non-commercial clinical trials to apply for EU funding, or to relax the requirements on forced collaboration or the involvement of SMEs. This is also traditionally where national governments and powerful vested interests indulge in the sort of tit for tat horse-trading that so often reduces initially coherent proposals to ineffective and unworkable legislation – for which they then turn round and blame the Commission.

Some governments, including Germany, are threatening to cut back their domestic research budget to finance the increased contributions being requested by the EU – in fact so far only the UK has given a commitment that it will not do this. Governments may also not be very open to suggestions that researchers should be freed from their onerous reporting requirements and the relationship should be one based on "trust" – in fact many have spent recent years insisting the Commission tighten up its accounting and reporting requirements, following accusations of massive waste. There are also plenty of vested interests who may not be keen to see a strong European Research Council with the authority and independence to follow a purely research-driven agenda.

The cancer research community will need to make its voice heard.

The home front

It is, however, at national level that the future of European cancer research will be decided. The contribution made via the EU research programme, after all, accounts for only around 6% of the total spending on cancer research in Europe, although this proportion will increase in 2007.

More importantly, it is within national academic and health systems that Europe's young researchers are nurtured. The career prospects, research opportunities and general culture within these systems are key determinants of whether scientists stay or head for the US, and whether clinicians get involved in clinical and translational research. One consistent complaint from cancer doctors throughout Europe is how few incentives there are for clinicians to do research, particularly outside the top research institutes and teaching hospitals.

Cardoso fears, for instance, that many centres will not be able to participate in MINDACT because of lack of back up, and that there will be some European countries with no centre taking part. "Research should not be looked at as something of a luxury that smaller hospitals shouldn't even think about it. Most important is a change of mentality among the people who decide where the money goes and those who run the hospitals. In almost all centres, doctors and nurses who want to do research have to do it in their spare time. There is no time dedicated to research within your working hours, so you have to work double for the same pay."

Sullivan, of Cancer Research UK, calls for the promotion of a "research culture". "You have to have the same pro-research message at every level, from the funders and government all the way through to the front-line of cancer healthcare delivery and universities. It's not something you do for a couple of weeks and hang it up. You have to carve out extra time and offer

real career pathways that reward clinicians and scientists for their research work. The funding environment needs to foster a research oligopoly where there is both competition and cooperation. It also needs to support research that challenges prevailing dogma."

He hopes that European governments will follow the UK and France and set up bodies that can take a strategic approach to national cancer research. The creation of the UK National Cancer Research Institute in 2001 opened the way for joint initiatives by the main non-commercial funders, which can address the research infrastructure, clinical research and basic cancer research in a coordinated manner. Over the past few years, the proportion of UK patients enrolled in clinical trials has increased from around 3% to 11%. A similar approach in France led to the creation of the Institut National de Cancer (INCa) as part of the French Cancer Plan of 2003. While Germany and the Netherlands have excellent cooperative groups and some outstanding research institutes, there are no other national strategic cancer research bodies. This not only hampers the organisation of cancer research at a national level, but deprives researchers of the voice they need to get governments and the EU to take cancer research more seriously.

LISBON TRIUMPHANT?

There is more at stake here than who will lead the world in genomics and biotechnology for health. Investing – or failing to invest – in research has a direct effect on standards of care and the survival of Europe's cancer patients. For instance, one consequence of pharmaceutical investment moving to the US is that Europe's patients have to wait up to three years for new cancer drugs to clear regulatory hurdles. Conversely, European patients have benefited from early access to groundbreaking techniques pioneered in European treatment centres, including adjuvant chemotherapy, breast conserving surgery, conformal radiotherapy and meso-rectal excision in colon cancer.

More generally, studies have shown time and again that patients treated within clinical trials do better – whether they are in the experimental or the control arm. Participating in clinical trials is also good for hospitals. It encourages clinical staff to take a more critical approach to their work, and it promotes multidisciplinary working and teamwork.

The logistical demands can lead to lasting improvements in the way service delivery is organised. Indeed, joining an international clinical trial can be a very effective way to raise standards.

However, arguments about the quality of patient care may not be enough to win debates over research budgets, because Europe's research agenda is driven by economic rather than healthcare considerations. And traditionally, it is basic research that has been relied upon to fuel European growth, as biotechnology SMEs take discoveries made in the labs and develop them into marketable applications.

However, as the MINDACT trial demonstrates, developing applications for all the '-omics' requires work with patients, and that requires collaboration with hospitals and clinicians who recruit, enrol and follow-up the patients, and provide tissue and blood.

This is research that Europe is uniquely equipped to undertake. Not only is Europe strong in biomedical research – the European Molecular Biology Laboratories in Heidelberg, Germany, and Cancer Research UK have been rated two of the three top centres in the world – but its public health systems offer an environment supportive of collaborative work that is unparalleled anywhere in the world.

The capacity of Europe's medical researchers to communicate and collaborate between hospital departments, between treatment centres, and most challenging of all, between hospitals and laboratories is widely recognised and is a huge strength. It explains in part why, despite poor funding and heavy regulation, the MINDACT trial is happening in Europe and not in the US. This capacity gives Europe the potential to lead the world in developing applications from the rapid advances in molecular biology.

By raising investment in cancer research closer to US levels, and above all by supporting clinical cancer researchers, the EU and national governments would be playing to Europe's strengths, which will be essential if the EU is to stand a chance of winning the global race to become "the most competitive and dynamic knowledge-based economy in the world." They would also ensure that Europe's patients gained access to the best quality treatment in the world.

Failing to fund research directly affects standards of care and survival of Europe's cancer patients

Finding the viral link: the story of Harald zur Hausen

Peter McIntyre

German virologist Harald zur Hausen was convinced by the early 1970s that the skin wart virus, human papilloma, was implicated in cervical cancer. Thirty years later we stand on the threshold of a vaccine to prevent this major killer of women. Looking back, it could have happened earlier…

Two pharmaceutical giants recently announced sensational results from clinical trials of vaccines that could prevent at least 70% of the 470,000 cases of cervical cancer globally each year. Cervical cancer kills 230,000 women a year, eight out of ten of them in developing countries, where it is the most common cancer in women.

In November 2004, the GlaxoSmithKline HPV vaccine study group delivered the results of a three-year study of a vaccine to protect against human papilloma virus (HPV). They reported in *The Lancet* 100% efficacy against persistent HPV 16 and 18 infection, the two types most closely associated with cervical cancer. The team called for long-term follow-up to confirm that this would prevent cervical cancer, but concluded "our data provide compelling evidence that the HPV 16-18 vaccine is highly efficacious" and "appeared to be safe and well tolerated".

Last month, at the 22nd International Papillomavirus Conference in Vancouver, a team from Merck reported that their vaccine had shown 90% protection against HPV 6, 11, 16 and 18. Alex Ferenczy, from McGill University, one of those involved in the Merck trial, said: "These are very exciting times for all of us in the field of cervical cancer prevention." His colleague Philip Davies, head of the European Cervical Cancer Association, went further. "We have the means to virtually eliminate cervical cancer."

Amongst those present in Vancouver was Harald zur Hausen, from Heidelberg, who can see the development of these vaccines as a vindication of his lifetime's work, and could be forgiven for thinking that this could have happened some years earlier. It was zur Hausen who first showed that the papilloma virus is the most significant cause of cervical cancer, and he stuck to his beliefs through years of confusion when the role of viruses was largely discounted.

A life's work

When Harald zur Hausen qualified as a doctor in 1960, the role of viruses in human cancers was unknown.

The first tumour-inducing virus had been dis-

"I fished the letter out of the trash can, and went to Philadelphia"

covered in 1911. Peyton Rous at the Rockefeller Institute for Medical Research in the US had isolated, from chickens, Rous sarcoma (retro)virus (RSV), which caused tumours in animals. Rous went on to pioneer research into the rabbit papilloma virus and its interactions with chemical carcinogens in the 1930s, and received a Nobel Prize for his work in 1966. In the early 1960s Ludwig Gross in New York demonstrated that retroviruses caused tumours in mice and rats.

zur Hausen's interest in infectious diseases and microbiology began when he was a student doctor in the 1950s. "Maybe it is the difficulty of the problems that fascinated me. I was certainly interested initially in the infectious causes of diseases, rather than cancer." In 1961, his first job was at the Institute of Microbiology in Düsseldorf, where he spent three years trying to induce a vaccinia (cowpox) virus to produce chromosomal breaks in mouse cells.

"This virus and many others did something to the chromosomes, but nothing very characteristic. I didn't get very much help because nobody else was interested in that question in that place. They just left me to it. At a much too early stage I was very independent and without sufficient background in the field."

He took courses in cytogenetics and molecular biology and taught himself to do lab work. "I got increasingly frustrated with my situation," he recalls. "After much too long, I decided to look for a position somewhere else."

The audience listened to zur Hausen in stony silence, and dismissed his (now vindicated) results

Then came one of those random mutations that seem to influence most successful careers. The School of Medicine at Pennsylvania University wrote to the Institute asking for a young German Fellow to come and work in the US. The Director threw the letter away, but later mentioned it to the young colleague with the interest in vaccines. zur Hausen did not hesitate. "I fished the letter out of the trash can, and went to Philadelphia."

There, renowned virologists Werner Henle and his wife Gertrude Henle were studying the Epstein-Barr virus, which had been observed the previous year in the UK in cultured Burkitt's lymphoma cells, using an electronmicroscope. The virus induced changes in human chromosomes and zur Hausen found the work interesting and intriguing. "The Henles very gently showed me what I did not know and I gained a lot of technical expertise and experience."

He used nucleic acid hybridisation to analyse DNA, and a fluorescent test developed by the Henles to detect the virus in a very few cells.

The Philadelphia experience inspired him, but zur Hausen disputed the view, held by the Henles, that cultured Burkitt's lymphoma cells maintain a persistent infection, in which a few infected cells transmit the virus to a small number of others.

zur Hausen's view was influenced by lysogenic bacteria, where the DNA of a bacteriophage persists in all bacterial cells and may become activated to produce virus in an occasional cell. He speculated that Epstein-Barr virus may persist in all Burkitt's lymphoma cells but become spontaneously activated only in a very limited number of cells.

After three years, zur Hausen was offered his own laboratory at the Institute of Virology in Würzburg, and he returned to Germany, determined to put his theory to the test. After a long and difficult struggle he was eventually able to show that "non-virus-producing" Burkitt's lymphoma cells contained the Epstein-Barr DNA. "We showed for the first time that viruses can persist in human tumour cells as genomes, and probably modify via the genomes these cells into tumour growth." It was not entirely unexpected to find signs of the virus in lymphatic cells, since Epstein-Barr virus can cause mononucleosis, a disease that involves the lymph nodes. But, zur Hausen and his colleagues were also able to demonstrate the virus in cells taken from a nasopharyngeal tumour, an epithelial carcinoma.

Steady approach

By the end of the 1960s, zur Hausen had a growing reputation. However, his careful, rational approach was not always heard in an age with huge appetite for social and scientific advances and in a field which seemed to induce wild optimism or profound scepticism.

The youngest of four children, as a young child near Essen in the final years of the war, Harald had witnessed the destruction of this industrial part of Germany in daily bombing raids. For young people in post-war Germany life was a serious business, and the zur Hausen children focused on their studies. Later, the hedonism of the late 1960s passed him by. "I was in places in Germany that were very quiet or in Philadelphia. I was not so much part of the 1960s. I was never a hippy," he recalls.

Perhaps this helped him to keep his feet on the ground.

At Würzburg he became increasingly sceptical about claims that cervical cancer, which was clearly sexually transmitted, was caused by the herpes simplex virus.

In 1972, at the age of 36, he was appointed Professor of Virology at the University of Erlangen-Nuremberg in Bavaria, and set up a programme to examine other candidates, including the papilloma virus (HPV), responsible for

VIRAL CANCERS

Viruses are strongly associated with about 15% of the global burden of cancer.

- Human papilloma virus with cervical cancer
- Hepatitis B&C with liver cancer
- Epstein-Barr virus with Burkitt's lymphoma and nasopharyngeal cancer and lymphomas
- The human T-cell lymphotropic virus (HTLV1) with adult T-cell leukaemia
- Human herpes virus type 8 (HHV-8) with Kaposi's sarcoma

A viral aetiology is also suspected for other lymphatic cancers, leukaemias and some brain tumours. Other tumours are linked to bacterial and parasitic infection. *Helicobacter pylori* is a major cause of gastric cancer, and parasitic liver flukes are responsible for a significant proportion of liver cancers in South East Asia. Globally, infections cause about 20% of cancers, but they are not evenly spread. In sub-Saharan Africa and parts of Southeast Asia about 40% of cancers are acquired through infections. In Western Europe and the US it is more like 10%.

skin warts. This cannot be grown in tissue cultures and is difficult to isolate from clinical specimens such as genital warts, where it exists in very low particle concentrations.

They were able to extract papilloma DNA from virus particles in the plantar wart (verruca). To zur Hausen's disappointment, these did not react to the genital warts, implying that the viruses must be different. Nor did they react to other skin warts which contained the virus. He was discovering that papilloma is not a single virus but many. This heterogeneity was also demonstrated in Paris. Today, we know of 106 different genotypes of papilloma virus and there are probably more to come.

At the time, much of the work on viral causes of cancer was being conducted in the US, under the Virus Cancer Program that had been set up in 1964 by the National Cancer Institute with a budget of US$50–60 million a year. This work focused on retroviruses, following the discovery of the feline leukaemia virus in cats, the bovine leukaemia virus in cattle and the ability of retroviruses to induce cancers in rats and primates.

This work eventually led to the discovery of oncogenes, but DNA virus research was neglected and poorly done.

In 1973 the US National Cancer Advisory Board set up an investigation into the Virus Cancer Program, which criticised its lack of attention to DNA viruses, the fact that grants went to a limited number of laboratories, and the way that researchers could vote money to each other. The report was designed to refocus the programme, but the message that went out to the public was that most research into viruses and cancer was a waste of money.

Low point

In 1974, zur Hausen went to an international conference in Florida to present results showing that herpes simplex was not present in cervical cancer. Shortly before he was due to speak, a researcher from Chicago announced that he had isolated 40% of the herpes simplex genome in one cervical cancer specimen. The audience listened to zur Hausen in stony silence, and dismissed his (now vindicated) results as lacking sensitivity. It was the low point of his professional life.

In 1977 zur Hausen took the Chair at the Institute of Virology at Freiburg. His team was able to extract and type virus material from a genital wart. Disappointingly, this type (HPV 6) was not present in cervical cancer cells. Soon afterwards the team isolated HPV 11, and found distantly related sequences in a cervical cancer biopsy. Next, Mathias Dürst, then a student at the Institute, succeeded in cloning a new type, HPV 16, from a cervical cancer biopsy. They were immediately able to show that this was present in about half of cervical cancer biopsies. The Institute then isolated HPV 18,

In 1984, pharmaceutical companies turned down zur Hausen's request to work on an HPV vaccine

responsible for another 17%–20% of cervical cancers.

In 1983 zur Hausen became director of the German Cancer Research Centre (Krebsforschungszentrum) at Heidelberg, and he gave over much of his time to refocusing the way that the research was done, introducing peer review, and breaking down barriers between separate research institutes. He encouraged researchers to rely less on mouse models and to work more closely with clinicians. He launched clinical co-operation units with University hospitals and in the last two years of his directorship, established the foundation for a comprehensive cancer centre with the University of Heidelberg.

In 1984, more than 20 years ago, zur Hausen approached pharmaceutical companies to work on developing a vaccine against HPV, which he was now convinced caused the vast majority of cervical cancers. "The viruses had quite a simple structure and it should have been possible to produce something. But the companies I approached did not believe that this would be profitable and said there were more urgent problems to be solved."

In the mid-1980s the polymerase chain reaction (PCR) 'democratised' genetic research, putting a quick and easy method for copying DNA fragments within reach of biologists with little training in molecular biology or how to prevent cross-contamination of results. Laboratories all over the world began reporting HPV 16 in all kinds of tissue.

Lost opportunity

These errors were enough to close the window of opportunity to hunt for a vaccine. zur Hausen says: "People became sceptical about the role of papilloma viruses in cancers. Pharmaceutical companies were not interested in the story any more, because this period created such confusion. I got a bit frustrated in this period and could not hide it. Cervical cancer is one of the major cancers worldwide, and it kills relatively young women. If our original conviction that this virus must be causative had been carried through, we would have made an earlier start on a vaccine."

By 1991, a number of epidemiological studies confirmed that the papilloma virus was indeed the causative agent for cervical cancer.

In March 2003, now highly decorated and honoured, zur Hausen retired as director of the Krebsforschungszentrum. He continues to work at the centre where his wife Ethel-Michele de Villiers, a Professor of Virology, keeps a depository of all 106 known papilloma types. This allows him what he calls "the privilege of friendly interference".

The Centre is still devoted to the aetiology of tumours, searching for viruses in leukaemia and lymphoma, especially the 80% of cases of Hodgkin's disease that do not contain Epstein-Barr virus. zur Hausen is researching lymphomas and leukaemia in children, for which a clean home and protected environment are risk factors, while poor hygiene and day care are protective. He believes that the intermittent infections that children acquire in less protected environments disrupt the build-up of the persistent infection which can lead to leukaemia.

He is also interested in how the normal protective mechanisms that the body has against the creation of 'immortalised' cancer cells are turned off one by one. The immune system, a system to block viral oncogenes and the ability of cytokines to render tumour cells harmless are all normally highly efficient, and they have to be switched off. It takes a long time for this to happen, but tumours have plenty of time. Infection with papilloma virus often occurs between the ages of 15 and 22. Cervical cancer is most common between the ages of 40 to 45. This 20-year period is sufficient for the genetic legacy of the virus to disarm cell growth regulators one by one.

Clearly the virus is not the whole story. Because, while men too have the virus, rates of penile cancer are barely 5% of the rates of cervical cancer. It is possible that oestrogen stimulates virus-producing cells and the 'immortalisation' of cancer cells.

Unanswered questions

Other factors such as smoking make cancers more likely, but zur Hausen believes that the papilloma virus will do it alone, given time. "People say that the papilloma virus is a necessary but not a sufficient factor. We here are deeply convinced that this statement is wrong; that the virus is necessary and in quite a number of instances is also sufficient. Modifications in the host cell genome can of course occur due to chemical or physical carcinogens, but they also occur due to the mutational activity of the viral oncoproteins themselves. Their long-term expression leads to that accumulation of mutations which may lead to tumours.

"Provided you give it time and provided it is not cleared by the immune system, then the risk is high that a woman develops cancer. We see today that the previous strict separation between chemical, physical, and biological carcinogens is nonsense. There is a very close inter-relationship between these factors."

A few scientists still report cervical cancer without papilloma virus. zur Hausen will believe it when he sees it. "I frequently ask colleagues to provide us with tumour samples which are in their opinion negative and we have never got any."

Known HPV types account for about 90% of cervical cancers, and it is possible that others are each responsible for a small part of the total. Some 'low-risk' HPV types, such as 6 and 11, very rarely can also cause other cancers.

zur Hausen believes there will eventually be one vaccine covering almost all the high-risk papilloma virus types. However, he fears that drug companies will price vaccines out of the reach of developing countries. Researchers at the Krebsforschungszentrum continue to look for cheaper alternatives, especially one that could be delivered through a nasal spray rather than by injection.

The papilloma vaccine is not the first to protect against cancer. "Hepatitis B in my opinion is the first anticancer vaccine, although it was developed to prevent the symptoms of acute Hepatitis B," zur Hausen points out.

Taiwan introduced a Hepatitis B vaccination programme in 1985. A study in 1995 showed a dramatic reduction in Hepatitis B infection amongst vaccinated children, and Taiwan is beginning to see a reduced number of liver cancers in teenage children.

zur Hausen believes that vaccines could substantially reduce the risks of cervical cancer over the next 20 years, and that targeted chemotherapy will be effective for those who already have invasive cancer.

He has spent his working life finding the evidence to show the role of papilloma virus, and although the road has been long and tortuous, he does not regret staying with it.

"Some of my colleagues think I am a bit stupid because I followed one thing for the whole of my career – the infectious agents for carcinogens. Many of those who worked with me in the early days changed to do something else. I believe that these chronic diseases demand a persistent involvement from the scientific side."

zur Hausen is preparing a major text book on infectious causes of cancer. The story he has been telling for 30 years is now broadly accepted as correct, but he believes there is more explaining to do. "I am relatively quiet and not an immediately aggressive person," he says, "but I think I can persuade people to do what is necessary".

"I believe that these chronic diseases demand a persistent involvement from the scientific side"

Glioblastoma: two studies herald a new start

Alex Mathieson

Surprise results of a temozolomide trial, and a new marker predicting who will benefit, offer hope for progress in the treatment of a highly aggressive brain tumour.

An international clinical trial has revealed that the addition of the chemotherapy agent temozolomide to radiation therapy increases survival in patients suffering from glioblastoma. And a companion laboratory study has offered hope of even greater improvements in survival in the future through identification of a molecular change in the tumour that allows prediction of benefit from the new treatment.

The combined work, published this March in the *New England Journal of Medicine* (vol 352, pp 987-996; 997-1003), is being seen as a significant breakthrough in medical research for patients with glioblastoma. In an accompanying editorial (pp 1036-1038), Lisa DeAngelis, Chair of Neurology at the Memorial Sloan-Kettering Cancer Center in New York City, hailed it as 'a new beginning' in chemotherapy for brain tumours.

Glioblastoma is the most common type of primary malignant brain tumour. It tends to occur in younger men and women, with around 20,000 new patients being diagnosed each year in the European Union. Patients have an average life expectancy of one year with the standard treatment of surgical resection followed by radiotherapy. The trial aimed to find out whether this could be extended without deleterious impact on quality of life through adding temozolomide to radiotherapy, both concomitantly and as an adjuvant treatment.

The clinical trial was performed for the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group. Almost 600 patients from 85 centres who had newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone or radiotherapy plus temozolomide (see box).

Results showed 26.5% survival at two years in those treated with the new combined therapy, compared to only 10.4% in those receiving radiotherapy alone.

The dramatic improvement in median survival at two years has surprised even the investigators.

Martin van den Bent, a member of the research team based at the Daniel den Hoed Oncology Centre in Rotterdam, the Netherlands, said: "Temozolomide is a new drug increasingly being used with patients undergoing radiotherapy, and this makes it an interesting candidate to

THE TRIAL

A total of 573 patients were randomly assigned to receive one of the following treatment options:

- Radiotherapy alone: focal irradiation in daily fractions of 2 Gy given five days per week for six weeks, to a total of 60 Gy
- Radiotherapy plus continuous daily temozolomide: 75 mg/m^2 body-surface area per day, seven days per week from the first to the last day of radiotherapy, followed by six cycles of adjuvant temozolomide at a dose of 150–200 mg/m^2 for five days during each 28-day cycle.

The median age of the patients was 56 years, and 84% had undergone debulking surgery.

Martin van den Bent: The combined treatment has become accepted as standard in glioblastoma in a very short space of time

investigate, but we had assumed that the study would be negative – the outcome was a surprise for us."

An earlier meta-analysis of around 3,000 patients had shown only small benefits from adjuvant chemotherapy, raising controversy about its use. The new trial seems to have cast such doubts aside and is changing practice in a dramatic fashion in van den Bent's home country.

Improved access

"Prior to the publication of this study," van den Bent says, "access to adjuvant chemotherapy for patients with glioblastoma depended on which country they were treated in. Those in the Netherlands or UK wouldn't get it, while those in Germany, France and the US would.

"Since the study, most patients in the Netherlands with glioblastoma who are candidates for treatment have been getting the combined modality treatment. It has become accepted as the standard for these patients in a very short space of time."

A key concern of any new chemotherapy treatment is that it should not significantly worsen patients' quality of life. The trial has found no such effects with the addition of temozolomide.

"Analysis of the seven most important quality-of-life domains, such as social functioning, shows no difference with the combined modality treatment," van den Bent explains. "This was also the reported experience of participating physicians – we were really amazed by the ease with which patients tolerated the treatment. Many of the side-effects suffered, like fatigue, occurred as a result of the radiotherapy, not the temozolomide."

Cost is another important element, and while van den Bent concedes that the combined modality treatment is more expensive, it may be the case that costs are shifted within the treatment programme rather than dramatically increased overall.

"Some patients will now have chemotherapy early in their disease process rather than later, so there may be a shift of costs from late to early," he says.

A health economic analysis is currently being undertaken to establish the impact of the new intervention on total treatment costs.

Predictive marker

The companion laboratory study, led by Monika Hegi of the Laboratory of Tumour Biology and Genetics at University Hospital, Lausanne, offers the promise of even greater impact of the combined modality treatment in the future.

The study found that patients who had glioblastoma that contained a methylated MGMT (O^6-methylguanine-DNA methyltransferase) promoter benefited from temozolomide, while those who didn't showed less benefit.

Identifying this specific molecular change is a complicated process, and no simple test is currently available. Van den Bent is hopeful, however, that following further trials, a test will be ready for the market in late 2005 or early 2006.

In the meantime, he and his colleagues are continuing their investigations, with the aim of further refining the combined modality treatment to improve survival even more.

"We are launching three new trials that will look to improve this now-standard treatment in several ways," he says. "One is intensifying the adjuvant part of the treatment, another is prolonging it, and the last is to add other drugs to the combination. These trials are being initiated right now."

The dramatic improvement in median survival at two years has surprised even the investigators

A healthy diet is simply a matter of good taste

Peter McIntyre

When cancer patients lose their appetite, serving food they like eating, at the time they want to eat it, is more effective than prescribing healthy meals that end up left on the plate.

People who undergo treatment for cancer often lose interest in food just when their body most needs to build its resilience and strength. Dieticians recommend that people with cancer eat small helpings and tasty snacks, and that they choose high-fat foods which pack a lot of calories into a small portion.

Their advice may seem counterintuitive to those of us concerned about 'healthy eating' and obesity. While, in general, plenty of fresh fruit and vegetables are recommended for healthy living, cancer patients may need to change their thinking, and focus on getting enough to eat. Amongst the advice, for example, in a Royal Marsden guide for cancer patients[1] is to add extra butter, margarine or oil to bread, potatoes and pasta, choose thick and creamy foods such as full-fat yoghurt, eat fried food more often and avoid filling up on low-energy foods like vegetables and fruit.

When someone is admitted to hospital for surgery, chemotherapy or radiotherapy, this advice may be hard to follow. Hospitals are institutions, and institutions have regimes and timetables that rarely allow patients the flexibility to eat when they feel like, or to follow a whim. Dieticians may prescribe delicious and nutritious diets, but hospital kitchens are not always equipped to prepare them, and the time it takes to process meal requests could mean that the food reaches the patient after they have changed their mind, or even left the hospital.

The Netherlands Cancer Institute – Antoni Van Leeuwenhoek Hospital in Amsterdam (NKI-AVL) was no exception. Patients had to order their meals two days in advance and meals were served three times a day in the wards. A patient who had undergone chemotherapy on a Monday had to work up some enthusiasm about what they would want for lunch the following Wednesday.

When the specialist centre – its particular strengths are breast cancer, melanoma and genetics – was given the green light in 1999 to build a new 180-bed hospital, they were told that they could not even have a full in-house kitchen, but only a 'cook-chill' system, which would be used to heat up meals that had been pre-prepared off-site.

1. *Eating well when you have cancer*. Royal Marsden NHS Foundation Trust. www.royalmarsden.org

This restaurant at the Netherlands Cancer Institute – Antoni Van Leeuwenhoek Hospital is designed to encourage patients to eat. You can wander in at any time between 7.00 am and 8.30 pm and choose from a variety of snacks and meals

Food for thought

Managers, dieticians, nurses and doctors decided it was time for a rethink. People with cancer come for in-patient treatment from all over the Netherlands, and staff felt it was important that their stay should be as pleasant an experience as possible under the circumstances, with an atmosphere that would be as homely as possible.

The in-patient design was for three floors, each housing three 'wards' of 16 beds in single and double rooms. So it was decided to add a restaurant area on each floor which would offer hot meals and snacks throughout the day.

Since the new hospital opened in September 2003, patients have been able to visit their nearest restaurant at any time from 7.00 in the morning to 8.30 in the evening, and find a good choice of hot food. They are encouraged to break out of meal times, and snack when they want. 'A la carte' has replaced 'plat du jour'. And today nurses and dieticians are not as concerned about the content of meals as about patients eating enough.

Petra Tuyp, head of facility services at the hospital, said: "We used to share the opinion that the cancer patients needed a special diet. But we had a lot of discussion with the dieticians and the doctors and we talked to the patients. We decided that it was more important to eat something than to eat nothing. Calories are more important than vitamins."

Since the hospital opened, surveys show that patients prefer chips to boiled potatoes, and if that is what gets them eating, then that is fine.

And so while menus in the restaurant include salmon and spinach, patients can also choose burgers and chips. "If you are ill, you may choose what you think is the nicest tastiest food rather than what you believe is the healthiest. If the patient likes fish and chips, for example, it is more important they eat this, than be served with vegetables they will not eat."

The new system costs more. There are three restaurants and they each have to be staffed. However, food costs have remained the same and the number of meals served has risen by 10–15%. Tuyp says that they were disappointed by this modest increase until they looked at how little they were throwing away every day. "Under the old system, we served every patient three meals a day and we served a lot of food that was not eaten. Under the new system all the food we serve is eaten."

If the patient likes fish and chips, it is better they eat this than be offered vegetables they will not eat

Popular

The new system is popular with patients. "The most important thing is how the patients feel in hospital, and that they can stay in as normal an environment as possible. Our surveys tell us that they feel that the new system is very good and that they feel very cared for."

Not that the new system has been without problems. It took time for patients to adjust to the "eat as much as you like, when you like" message.

They tended to go to the restaurant only at traditional meal times. Now nutrition assistants visit the wards with lists that show patients what they could have. Patients are encouraged to take a snack mid-morning, and another at 4.00 pm, between lunch and supper.

Even bed-bound patients get a better deal than before, as they are able to order their meals two hours rather than two days in advance. They are served their meals in their rooms, although not at such flexible times as those who go to the restaurants.

Relatives too miss out on the benefits. Because patients come from all over the country, the NKI-AVL has a guest house for relatives to stay. But they cannot eat with the patients in the hospital restaurants. Tuyp accepts that this is a drawback. "We surveyed the patients and they said they would like their relatives to eat with them, but because of budget restrictions, we cannot offer food to the relatives in the restaurants, although on some occasions the nurses close their eyes to it.

"If relatives ate there we would have to double the number of meals. Also, patients are not charged for their meals. We are looking at whether it is possible to set up a system to charge relatives for meals."

Another issue that required attention was an initial lack of communication between nutrition assistants and nurses. That has been addressed and nurses are now given more information so that they communicate better with patients about what they can eat, and call on nutrition assistants if a patient has a problem.

Whatever you fancy

People receiving treatment and medication for cancer may be put off their food for many reasons. They may feel sick, and so not want fried food. Others may have a sore mouth or throat due to radiotherapy or chemotherapy, and so need to choose soft and smooth foods that slip down more easily, and not eat food that it is too hot. It is also possible for a cancer patient to have an altered sense of taste, so that foods taste bland or the patient has an unpleasant taste in his or her mouth.

The beauty of the new system is that whatever the dietician recommends, the patient will find something suitable on the menu.

In addition to regular patient surveys, research staff study the nutritional status of patients. However, it will never be possible to produce hard evidence that the new eating arrangements lead to better nutrition, especially as the average length of stay is gradually being reduced from five to six down to two to three days. Tuyp is content to know from surveys that the patients feel they have had a better experience. "There are many influences on your nutritional status, and it is difficult to say whether this makes a difference."

The proof is in the eating, and in the fact that nobody wants to turn back the clock. Tuyp says: "Changing the system is not under discussion at all. No one talks about going back to what we had before. Everyone is convinced that the new system is better for the patients. The doctors and dieticians are very enthusiastic. We have done this project together in cooperation with the dieticians, otherwise it would not work."

Follicular lymphoma: side-lined drug excites new interest

Janet Fricker

A study showing that follicular lymphoma patients benefit from adding interferon to standard chemotherapy has opened up new avenues for research.

A meta-analysis has shown that using interferon in addition to chemotherapy leads to longer periods of remission and longer survival in patients with follicular lymphoma. The study published in the April 1 issue of the *Journal of Clinical Oncology* (vol 23, pp 1-9) analysed data on 1,922 patients with follicular lymphoma, treated in the context of 10 phase III trials that had produced conflicting results.

Follicular lymphoma represents the second most common histological sub-type of non-Hodgkin's lymphoma (NHL), accounting for 35% of lymphomas in North America and 22% worldwide. The median age at diagnosis is 59 years, with the incidence being slightly higher in men than in women. "The median survival is 9 or 10 years, virtually irrespective of the type of treatment," said Ama Rohatiner, Professor of Haemato-Oncology at St Bartholomew's Hospital in London and the principal investigator of the study. "With conventional therapy, response rates are about 80%, but the illness virtually always comes back."

Treatments vary depending on age and stage at presentation, from a 'watch and wait' strategy in the initial stages to multi-agent chemotherapy. Treatment options in current use include fludarabine-based regimens, treatments containing anti-CD20 (rituximab/MabThera), radioimmunotherapy, and high-dose treatment supported by autologous haematopoietic progenitor cells.

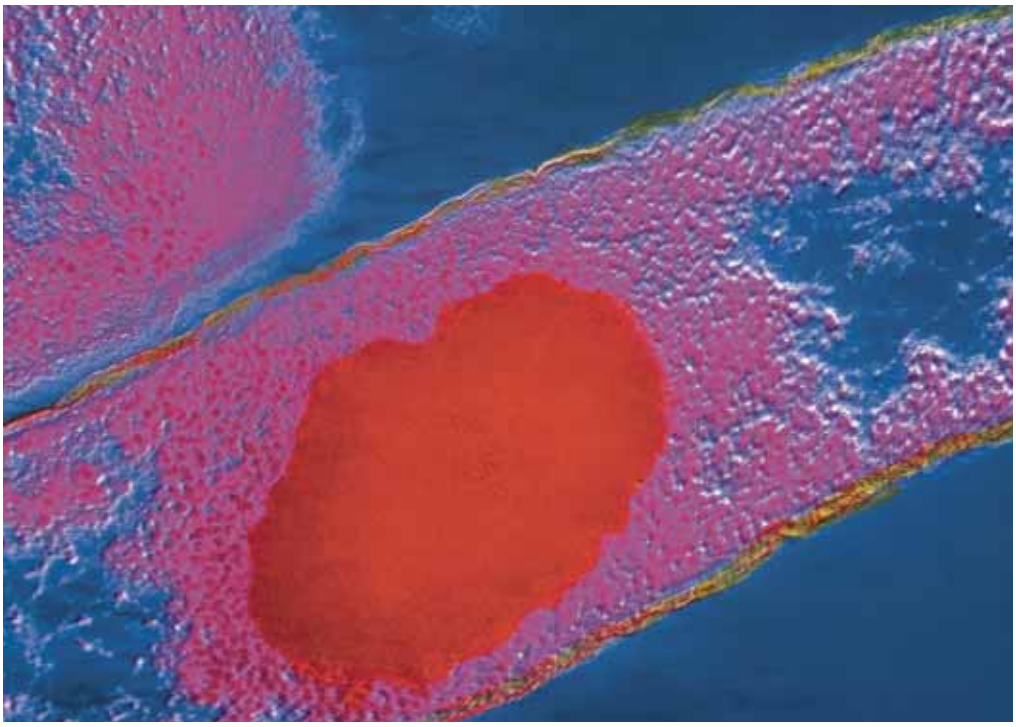
Yesterday's drug?

"Since the inception of the study, the use of interferon α-2 [IFN α-2] for follicular lymphoma has been largely superseded by these newer treatments" said Rohatiner. Patients today are rarely treated with IFN α-2 since its clinical toxicity is not negligible. It needs to be given by subcutaneous injection, and causes flu-like symptoms and fatigue. "But while the newer drugs cause fewer side effects, show higher response rates and longer durations of response, with the exception of high-dose therapy, they have yet to show an improvement in survival," she added.

The rationale for performing the meta-analysis came from a series of 10 randomised studies, published between 1991 and 2001, evaluating the use of IFN α-2 given in conjunction with chemotherapy to newly diagnosed patients. The problem was that considerable heterogeneity between studies led to conflicting results, which made it difficult to reach a consensus. Discrepancies in the results occurred even when only studies of similar design were considered.

- In some studies IFN α-2 was given concurrently with chemotherapy; in others it was used as 'maintenance' therapy, whilst in others it was used throughout.
- Chemotherapy regimens varied in intensity, from relatively low doses of alkylating agent (chlorambucil or cyclophosphamide) to doxorubicin or mitoxantrone-containing regimens. Doses and schedules of IFN α-2 also differed.
- Additional variability occurred because some studies allowed the use of radiotherapy to sites of bulky disease at presentation, or to residual disease.

The meta-analysis was therefore undertaken to clarify the effect of interferon on response, duration of response and survival. Investigators from the original studies were approached and asked to provide updated patient information, with only patients diagnosed with follicular lymphoma being included in the final



CNRI / SCIENCE PHOTO LIBRARY

E.coli synthesising human interferon

analysis. Chemotherapy regimens were categorised by the intensity of chemotherapy, with studies utilising relatively 'less intensive' chemotherapy being defined as those using chlorambucil, cyclophosphamide, or cyclophosphamide/vincristine/prednisolone (CVP) as initial therapy, whilst regimens using anthracycline or mitoxantrone-based combinations were considered 'more intensive'.

Overall, the study found that IFN α-2, when given in addition to conventional chemotherapy as part of initial therapy in newly diagnosed patients with follicular lymphoma, prolongs remission duration and survival, but does not result in any improvement in response rate. Exploring these differences in greater detail, the investigators found that interferon increased survival in patients in whom the drug was given in conjunction with relatively intensive chemotherapy, at a dose of at least 36 million units/month.

The authors acknowledge that, with the development of alternative treatments, it is difficult to know "how best to incorporate this information into the algorithm of therapy". Michele Ghielmini, Associate Professor of Oncology at the Oncology Institute of Southern Switzerland, agrees. "If rituximab didn't exist, this paper would have been enough to convince me to use interferon, but now it's probably a bit late to be helpful," he said.

But the study is valuable in that it points the way to future research. "We know that rituximab and chemotherapy is better than chemotherapy alone, and from this study that interferon and chemotherapy is better than chemotherapy alone, so perhaps we should now be investigating whether the combination of chemotherapy, interferon and retuximab in follicular lymphoma would be even better still," he said.

Interferon increased survival in patients when given together with fairly intensive chemotherapy