Cancerworld
Education & knowledge through people & facts

Number 3, December 2004

Lars Påhlman

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Published by
Editorale Darwin srl
Piazza Antonio Mancini, 4 - 00196 Rome

Printed by
IGER Istituto Grafico
Editoriale Romano s.r.l.
Viale C.T. Odescalchi, 67 - 00147 Rome

Cover photograph
Eligio Paoni /Contrasto

In attesa di registrazione presso il Tribunale di Milano

Direttore responsabile
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20122 Milan, Italy
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Cancer World is published six times per year by the European School of Oncology with an average print run of 12,000 copies. It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available on-line at www.cancerworld.org

Too valuable to put a price on

Kathy Redmond ■ EDITOR

Access to information is essential for scientific progress, yet in many places it remains very limited. Given how easy it is to post an article on the web, where it is freely available to anyone who has access to the Internet, the current system based on subscription journals is coming increasingly into question (see Focus, p. 61). Governments, who foot the bill for most university libraries, and the charity sector, who are important sponsors of cancer research, are foremost among those examining possible alternatives.

New models of publishing are already starting to emerge, which have the potential to give millions of people worldwide access to scientific literature.

Unfortunately, the debate between advocates of open access and the traditional bastions of scientific publishing has become increasingly polemical.

Proponents of the current system argue that many clinicians are drowning in literature and have no time to keep up to date with every development in their speciality. Journals provide a reliable filtering mechanism and a robust means of assuring the quality of their contents through their tried and tested peer-review system. Moreover, many scientific journals are published by professional societies who reinvest revenues from sales to help them fulfil their mission.

Advocates of the open access model, on the other hand, argue that the more accessible the findings of research, the more likely we are to avoid duplication of effort and promote research in areas where data need to be replicated. They also point to the vast amount of information already in the public domain, much of which is of questionable quality, and argue that free access to credible, peer-reviewed information is a public necessity.

In an attempt to find a workable compromise, a coalition of 49 not-for-profit publishers in the US, including AACR, ASCO and ASH, have proposed a model for the dissemination of scientific literature under which publishers would:

- Make important articles of interest available online at the time of publication
- Make the full text of their journals freely available to everyone worldwide either immediately or within months of publication
- Make the contents of journals freely available to scientists working in low-income countries.

Cancer World welcomes the US initiative as a sustainable basis for providing open access to scientific information.

Even though we are a magazine and not an academic journal, we post our articles on the Web within one month of publication. We urge European cancer societies to take similar steps to promote the widest possible dissemination of information in their journals.

Lars Påhlman: Super-specialist

Marc Beishon

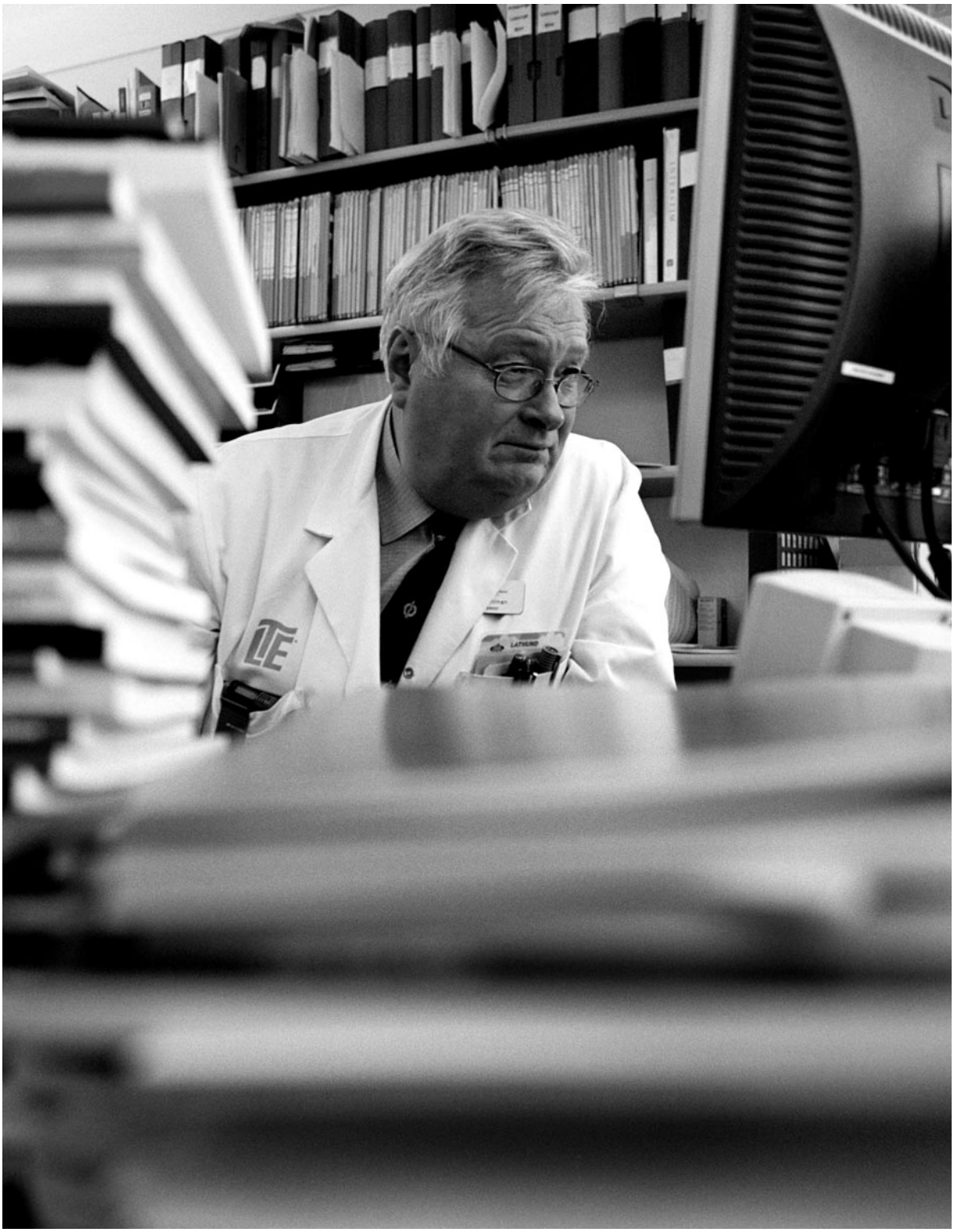
In 1982 Lars Påhlman became an early advocate for the importance of expert surgery in colorectal cancer, and he has been spreading the message ever since. More controversially, he believes surgical oncologists are a thing of the past: in future, cancer surgery – and ultimately radiotherapy and medical oncology – will be carried out by organ-based specialists.

First impressions can be deceptive in the medical world. Spend a few minutes with Lars Påhlman, Professor of Surgery at the University of Uppsala, Sweden, and you will quickly discover a complete dedication to his chosen field of colorectal surgery and research. You may even know that he has a passionate interest in stamp collecting – and conclude that he is a quiet, studious sort with his head buried in matters of proctology and philately.

Ten minutes later, however, and it is apparent that Påhlman is one of the more outspoken members of the medical community, both at home in Sweden and further afield. He is a man who speaks his mind – and holds strong views about the role of surgery in cancer treatment, the influence of the pharmaceutical companies and medical training for young surgeons. Of late, he has even been challenging the august teaching methods at the ultra-traditional Uppsala University medical school – something one could only do with the clout that comes from being one of the world's top colorectal surgeons and researchers.

Not that Påhlman's colorectal "super-specialism" – a label he agrees with – was his first choice. Like many top doctors, he made the most of opportunities that came his way in the early days. Born in 1946, he is one of five children, and the only one to follow his father – a surgeon turned GP – into medicine. Unusually for Swedish children, he attended a boarding school near Stockholm, but did not initially make the grades necessary to go to medical school. He first studied genetics for a year and a half at the University of Stockholm, and did his compulsory military service.

The genetics course raised his grades sufficiently to go on to the medical school at the University of Uppsala, not that his father was outwardly pleased. He said: "Don't blame me if you don't like it," comments Påhlman. Apart from making his grades he was – and is – "a very organised person. I never missed an exam and passed them all – I always read everything and have been well prepared for tests."



WENDY SUE LAMM / CONTRASTO

"I realised that evening that I'd almost killed a patient and thought I wasn't good enough"

However, he quickly earned a reputation for being outspoken. "Some didn't like me, as I'm not afraid to speak out and say what I think. A good example was when we did a course in social medicine – I didn't think it was worthwhile. When we were asked for feedback on the whole course I said the only good thing was a field trip where we saw the sun shining on a famous mountain near the Norwegian border. The professor wasn't happy." (That professor is now a firm friend – they are both avid stamp collectors.)

After medical school he did the traditional Swedish thing and went to complete his surgical training at a large district hospital in Falun, about 200 km north of Uppsala. But it was an earlier, shocking event that set him on a rather round-about way to obtaining a general surgery qualification.

"While I was a student I worked as a radiologist during the summer, and a patient I had injected with a contrast medium went into anaphylactic shock. I didn't even realise she was sick until the nurse who was helping me raised the alarm, and the patient survived. I realised that evening that I'd almost killed a patient and thought I wasn't good enough. But I was determined never to be afraid of a sick patient, so next summer I worked as an anaesthetist and then spent a year on this specialism, learning how to take care of critically ill people."

Needing to obtain experience in other areas, he then switched to orthopaedics for two years, thinking perhaps this branch of surgery would be his specialism, but he also had to complete general surgery training. Each new step he found more "fun" than the last – a word that speaks volumes about how rewarding he finds his work.

Påhlman returned to university in Uppsala to continue his academic career by writing a thesis and developing another specialism. This is a step most Swedish surgeons take, but the majority will then return to the regions as consultant surgeons. Not Påhlman. He wanted to stay involved in research, and he has remained at the University ever since. But he had to chose a specialism for his research. "I'd planned to go into vascular surgery, but there was no place for me. The best department at Uppsala was the endocrine group – but there was no room for me there either."

Then an epidemiologist suggested he look at rectal cancer. This was just the sort of challenge Påhlman was looking for – there were high local recurrence rates (i.e. local to the site of the cancer) after surgery, and tremendous scope for research about how to improve the gloomy outlook for many patients. His thesis was a wide ranging set of projects, as can be judged from the title – "Rectal carcinoma – an evaluation of the local recurrence rate, surgery for cure, staging and perioperative radiotherapy" – and in the 1980s he also began work on a randomised trial, and became a tutor for several other projects.

As he explains: "When I first became involved in rectal cancer in the late 1970s and early 1980s, local recurrence rates were between 30 and 50% – in the first paper I published, I reported 40%. We thought this was a matter of tumour biology, which is why we started to add radiotherapy to the treatment."

So convinced was he that his first big trial "flipped the coin", as he puts it, between pre- and postoperative radiotherapy. "Then in a meeting in Rotterdam in 1982 – which I remember well – I saw Bill Heald, a surgeon from Basingstoke in England, who told us he had no local recurrences at all – it was nothing else but good surgery. I was sitting there with an old surgeon, who said, 'He must be a crook – it's rubbish.'"

A year later, Påhlman was in the US at another conference and saw Heald again, this

time running a film about his operating technique for rectal cancer. After watching it several times, Heald eventually asked who he was. "I told him I'd published my first paper with that 40% local recurrence rate. Bill said something like, 'Oh my goodness, let's have a beer lad,' and I found out how to operate like him."

The technique pioneered by Heald at Basingstoke is total mesorectal excision (TME), which essentially involves sharp dissection of the tumour and surrounding fat under direct vision. TME has had an extraordinary impact on preventing local recurrence in rectal cancers suitable for the technique – the majority – and Påhlman and colleagues were quick to apply it to their patients.

"In my thesis I had a project to find local recurrences as early as possible, so I already had a follow-up programme using computer tomography, which was rather new then, and saw all patients after six months. I took biopsies and we had no recurrences because I'd learnt how to operate."

Together with long-standing oncologist partner Bengt Glimelius – who like most Swedish practitioners combines medical oncology and radiotherapy qualifications – they started to publish that there were no local recurrences in Uppsala. They found colleagues reacted in a similar way to those who heard about the Basingstoke work. "People were furious," says Påhlman; "they thought we were stubborn and were not being truthful.

"Then in 1986 I gave a talk to the Swedish Medical Society, having then operated on more than 90 rectal cancers, and I reported one local recurrence. An old surgeon stood up and said, 'This is the day I've been waiting for – now you report a recurrence. Now we believe you.'"

Påhlman's focus on the very best surgical techniques has certainly paid dividends in Sweden. After what he terms a "tough discussion" in medical circles about why he was getting such good results, he has led training across the country to ensure that only qualified colorectal cancer surgeons can carry out operations.

Hitting the ski trails with his friend and colleague Bengt Glimelius

Sweden, he says, now reports some of the best results for rectal cancer in the world, and other countries that have adopted similar strategies, such as Norway, are also doing very well. But the move to organ-based specialism is by no means well advanced in all countries – Påhlman mentions Switzerland and eastern Europe in this context.

"Now all Swedish surgeons have almost the same results," he adds. "When I meet young surgeons they ask me whether I know their local recurrence rates."

And of course he does – Påhlman is chair of a Swedish rectal cancer register and knows about every cancer that has been operated on and who carried it out. That is no mean feat, given that colorectal cancers are the third biggest killers after breast and prostate, and the country sees between 5,000 and 6,000 cases a year, at 50–60 per 100,000 population, and rising.

So with the TME technique and top-quality surgery, Påhlman and Glimelius realised that the

"This is the day I've been waiting for – now you report a recurrence. Now we believe you"

"One of the referees said: 'Don't accept this paper as it will ruin the economy for the radiotherapists'"

way forward lay not with radiotherapy, but a combination of surgery and radiotherapy (though of course surgery alone remains the single most important treatment). Påhlman's view is also that it is natural and desirable that surgeons – who have the closest involvement with patients – should be among the research leaders.

From the late 1980s onwards he has been involved with numerous, large randomised trials, notably the Swedish Rectal Cancer Trial, which he says was the first to demonstrate that patients receiving a week's worth of preoperative radiotherapy did better than those who did not. He was also an investigator on an important Dutch TME trial.

The Swedish Rectal Cancer Trial was eventually accepted for publication in the *New England Journal of Medicine* in 1997 – but as Påhlman comments, it posed a direct threat to some US interests, where longer (five-week) courses of postoperative radiotherapy have been the norm. "One of the referees said something to the effect of, 'Don't accept this paper as it will ruin the economy for the radiotherapists.'"

Påhlman is not complimentary about practice in the US, although he's quick to stress that some American professionals are good friends. "They rarely quote European articles, and our Swedish radiotherapy regimen has never been accepted. When an insurance company is paying they can drag out the money."

It is a loaded statement, but colleague Glimelius concurs, noting in a recent presentation that "non-scientific reasons dictate why long-course regimens are used [outside of trials]". Påhlman was also unimpressed by surgical techniques he observed a few years ago at some big US hospitals; a particular frustration is the wasted opportunities to conduct more trials. He mentions, as an example, the need for studies of pelvic pouch surgery for inflammatory bowel disease, to compare the effect on bowel function of taking the mucosa down to the anus versus leaving a small rim and stapling it. "In Uppsala we have done 300 such operations since 1982 – at the Mayo Clinic they do 300 a year, so it is a piece of cake to do research if they want."

He feels that a system where patients insist on finding doctors who "know all the answers" mitigates against such trials. He feels fortunate that, in the state-funded Swedish system, patients are more likely to trust the judgement of doctors who candidly say they do not know which treatment will be best – and that there is only one way to find out.

Not that all is rosy in Swedish healthcare – far from it. Often held up as one of the best systems in the world, demand has stretched resources such that waiting lists can be long (some operations such as varicose veins could take years), while Påhlman comments that primary care is not pulling its weight as it could – some GPs see as few as seven people a day, he comments.

However, waits for top priority cases such as cancers are still quite short and Påhlman says that once in hospital, treatment is generally first class. In part that is down to specialism – as Påhlman says, he does only colorectal surgery; he would not do a hernia or take out a gall bladder. There has, he adds, been a debate about the centralisation of surgical expertise and possible lack of emergency cover in remote regions. His view is that elective surgical expertise comes first, noting that you'd always take a Volvo to a Volvo garage for servicing – but a Saab station might do to keep you going for a bit if you broke down in the mountains.

His trenchant views on the role of surgery extend beyond Sweden, to the rest of Europe. In 2000 he was appointed President of the European Society of Surgical Oncologists (ESSO), and has set about trying to change the role of the organisation.

WENDY SUE LAMM / CONTRASTO

A particular frustration is the wasted opportunities to involve more patients in trials

The main issue for him is that top surgeons simply do not participate. "The real big shots in surgery are not on the ESSO board," says Påhlman, who has been a board member since the early 1990s. Instead, he argues, because of the move for doctors to specialise as organ-based surgeons rather than general cancer surgeons, they are more likely to be found on the boards and meetings of societies such as the European Pancreatic Club.

What's more, Påhlman thinks that in 10 years medical oncologists and radiotherapists will go the same – organ-based – way. His solution, which he has proposed to the Federation of European Cancer Societies (FECS) – where he has also been a board member – is to reorganise in organ-based groups. This did not make Påhlman popular at first, "but I think they understand what I mean," he says.

As for ESSO, he says the plan for the next congress – in Venice in 2006 – is to call it the "Congress of cancer surgery", instead of surgical oncology, and invite the various organ-based societies to participate. To ease them in, Påhlman says organ topics will be kept to a certain day to maximise value for attendees. He adds that since he stood down from ESSO, and his successor Luigi Cataliotti took over as President, he feels the shift in thinking at ESSO/FECS has continued as he would like, and says this is his major achievement at European level.

Putting his surgeon's hands to some carpentry work at his island summerhouse in Stockholm's archipelago

Another big issue with the role of surgeons is the lack of funding. As Påhlman points out, a good ESSO conference attracts several hundred surgeons, while equivalent events for medical oncologists can run to thousands of attendees. It's a similar picture at joint events – and this is because medical oncology benefits greatly from "drug money".

"For me, oncology has been dominated by drugs, and medical oncologists today have too much influence," says Påhlman. "It is the same for drug treatments in other fields such as cardiology and gastroenterology." Apart from the difficulty in enlisting patients into trials, he says that funding basic research to ascertain, for example, the relative merits of staplers used in colorectal surgery, is proving hard. Meanwhile, certain classes of drugs – he picks out antibiotics – are taking second stage to the development of drugs likely to prove more lucrative.

Then the sheer number of drugs entering the cancer arena is outstripping the capacity of doctors to know what to administer, adds Påhlman. However, for colorectal cancer he talks excitedly of the potential of the many drug treatments becoming available, and in general he considers his field to have as much if not more going on than other cancer types.

On the drug side he mentions Erbitux (cetuximab), which acts on epidermal growth factor receptors, and has been trialed with success in Europe with patients with advanced colorectal cancer (this was the so-called BOND trial); and also Avastin (bevacizumab), which acts on the vascular system [the two drugs are reviewed on p. 37 of this issue].

There is also much to gain, he adds, by heredity screening programmes: hereditary non-polyposis colorectal cancer (HNPCC) could be implicated in up to one in six colorectal cancers, and there is also familial adenomatous polyposis (FAP).

Indeed one of his key missions is to establish a colorectal cancer screening programme in Sweden – he has been lobbying the country's health policy makers for some time on this issue. "I'm fighting hard for the government to run a feasibility study, as has already been done in countries such as England," he says. "I'm known as Mr Screening for colon cancer in Sweden – I've said, 'Let's give all Swedes a colonoscopy as a 60th birthday present.'"

At Uppsala, Påhlman is certainly doing as much as he can to further research. "Today I have 32 randomised trials running in my unit," he says. "Large trials are my main research interest." They cover a wide spectrum of chemotherapy, radiotherapy and surgical treatments. Most of these trials are organised by Påhlman and colleagues within Sweden and with European centres, and they include four EORTC (European Organisation for Research and Treatment of Cancer) studies at present. However, Påhlman notes that Sweden has tended to carry out its own trials and has been on the periphery of European cooperation, a situation he would like to move away from.

Not all the research has proved as fruitful as the landmark study on preoperative radiotherapy. Work on predicting prognosis of rectal cancer patients came up against a brick wall in the mid-1990s, when all the markers and samples gained from tumours barely advanced the percentage of patients they could confidently predict (from 7 to 9%). This programme may be restarted, thanks to advances in translational research.

In common with most cancer researchers, Påhlman is alarmed by European and state rules governing informed consent for transla-

tional research, and for trials involving marketed drugs (on the latter, he says doctors are preparing a paper to be submitted to the Swedish government).

Away from research, Påhlman also runs the colo-proctology surgery training programme at Uppsala, and is chair of the European Board of Surgical Qualification for the speciality. His own surgeons get a special six-year training programme, where they carry out all four operative areas – cancer, inflammatory bowel disease, function and proctology – and become "leads" (or "cream positions" as Påhlman puts it) in each for certain periods, during which they can walk into the theatre and say, "I'm the cancer surgeon this month, that is my procedure." "Everyone stands back, except the consultant who holds the retractors while the young surgeon does the job," says Påhlman. This is certainly different from the usual assistant's role that many young surgeons play.

He's fiercely critical when he sees poor surgery in his own hospital – when he says that some surgeons should pay to come and work there, he is not joking. He has also witnessed the entire spectrum of practice all over the world as a visiting professor, including on training visits to the Baltic states.

There are some centres that have greatly impressed him – he cites St Mark's in London – but it is likely that most have much to gain from his expertise. When a Lithuanian surgeon visited Uppsala, Påhlman operated on a particularly difficult case, removing and replacing bladder, bowel and prostate, and providing a new rectum and no stomas. His visitor presumed that the patient was on a one-way trip to the cemetery and was astonished to see him sitting up in bed the next day.

Påhlman is still travelling a lot, although he now says he won't accept another European board position, as time simply won't permit it. He has three grown-up children – none of whom have followed him into medicine – while his wife works for an arts foundation. "She calls me a square," he says, thanks to being buried in papers and stamps. That's clearly not true all the time – wine, opera and an island retreat are also on the agenda.

He is though a highly serious philatelist, with British Empire stamps a speciality. A presentation he has given at medical conferences is a grand tour around the world of anti-tobacco stamps – from countries that have used their postage stamps to carry messages about smoking. Påhlman has scanned a remarkable number of stamps under various themes for this presentation, and you could well catch it being shown at meetings in southern Europe, where smoking rates are far higher than Sweden.

While he is doing his bit for prevention, solving surgical and treatment problems for benign disease and cancers remains Påhlman's core mission. Tracking back to medical training, he is now engaged with the authorities at Uppsala University in a bid to move towards problem-based learning and away from traditional classroom instruction (he cites McMaster University in Canada as an exemplar). "Most medical students are lazy," he comments, "just sitting there with their mouths open, waiting for the grilled bird to fly in." Well we get the gist – he wants a more demanding environment for students and faculty alike to prepare them for the challenges ahead.

And if he could wave a magic wand, it would be to eventually let those students loose on far more clinical trials – he estimates that just 3% of patients with rectal cancers, for example, are currently in trials in Europe. Work on "flipping more coins" can't come fast enough for Påhlman.

"Most medical students are lazy, just sitting there with their mouths open waiting for the grilled bird to fly in"

A good prognosis for progress in breast cancer

Mary Rice

Developments in adjuvant therapies, surgical techniques or genetic profiling are discussed in scores of forums throughout the year. But multidisciplinarity requires a broader view of progress in the field – and that was the aim of the Milan Breast Cancer Observatory, held for the first time this summer.

At the 6th Milan Breast Cancer Conference held this June, distinguished specialists were asked to read the stars to divine what the coming year would hold in store for the world of breast cancer. In a session entitled the Milan Breast Cancer Observatory, scientists, clinicians, a representative from the advocacy group Europa Donna and a health reporter from the national press presented their predictions for their own fields of work over the 12 months ahead.

The Conference is an annual affair, organised by the European Institute of Oncology, and attended by leaders in surgery, radiotherapy, medical oncology, basic science, pathology, biostatistics and clinical trials, from all over the world.

This was the first year to feature an Observatory session on the agenda, but it is intended to become an annual event.

The star-gazing exercise is designed to help conference participants to place their own work within the context of trends and developments in the wider field of breast cancer. This is becoming increasingly important as scientific progress is rapidly increasing our knowledge of the disease, particularly in the area of genetic profiling, with implications for pathology, diagnostics, therapeutic procedures and tailoring treatments. This rapid pace of progress, advised the Observatory's panel of experts, looks set to continue.

TARGETED TREATMENT

Gene expression profiles and proteomics were flagged up as the great white hope for the coming year. The expectation was that these would be able to lead to tailored treatment based not just on genetic signatures but also on such factors as types of cancer and age. Early efforts will be made to bring microarrays and proteomic signatures into clinical practice in order to create appropriate treatments for individuals.

Tumour markers and genetic profiles have a number of other uses: they can help improve treatment selection for pre-operative chemotherapy, which will allow more women to preserve their breasts. They can also be used to identify sub-groups of patients at high risk of recurrence in order to modify treatment. This may help select patients with ductal carcinoma in situ (DCIS) for treatment by excision alone, thereby avoiding radiation.

The distinction between endocrine responsive and non-endocrine responsive disease is set to gain wider

recognition as a major tool for planning systemic therapies for breast cancer. Sequential endocrine adjuvant therapies are likely to be confirmed as a valuable therapeutic approach in women with endocrine responsive disease, though further studies to overcome resistance to endocrine therapies by sequential treatments are needed.

There will also be new opportunities for improving the use of therapies for patients with advanced breast cancer by using the new targeted treatments together with cytotoxic agents. These compounds will reach the stage of testing in the adjuvant setting very shortly.

Progress is also expected in the development of novel agents with one or a few biological targets, using advanced molecular and immunological technology to overcome mechanisms of malignant transformation, infiltration and metastasis which are still unclear.

HORMONE-SENSITIVE CANCERS

Aromatase inhibitors are set to become the standard adjuvant treatment for women who have steroid-receptor-positive breast cancer, although warnings were raised of the need for special care in monitoring bone loss. Continuing refinements of adjuvant chemotherapy regimens are expected, paying particular attention to the selection of drugs and dosage, and to the treatment schedule.

In both developed and developing countries, clinical prediction for the appropriate use of tamoxifen in selected patients should become standard. This strategy will be essential to offset increasing healthcare costs.

SENTINEL NODE BIOPSY

Sentinel node biopsy is set to become the universal standard of care for node-negative stage 1 and 2 breast cancer. The procedure will also be used more frequently after neoadjuvant therapy when the axilla is downstaged to node-negative after treatment.

OVERDIAGNOSIS

Diagnostic histopathologists will apply criteria to avoid overdiagnosis of DCIS and other conditions with increased incidence rates. These increases have frequently been the result of including more minor changes, which, though similar, lack the intrinsic risk of local recurrence and evolution to the invasion of lesions that define the importance of DCIS. The level of threat to survival represented by different local and distant recurrences, including the time dependency of survival in high-grade, rapidly proliferating cancers, will be more precisely defined.

The increasing incidence of 'inflammatory carcinoma' will be significantly reduced by careful application of diagnostic criteria – an effort already begun by quantifying the degree of breast involvement by inflammatory changes. The importance of clustering in analysing standard data will become more widely recognised.

BIOSTATISTICIANS

How will all this be held together? Strengthening the collaborations between biostatistical scientists and clinical and laboratory scientists will be a critical part of achieving progress. Computation biology plays an increasingly important role in defining the molecular basis of disease and identifying targets for therapeutic intervention. Equally important for patient care will be the thoughtful application of current clinical trial methodologies to tailor trial design and analyse results separately for subpopulations of patients according to the steroid hormone receptor status of the primary tumour.

PATIENT PARTICIPATION

There will be a growing recognition of the contribution that patient advocates can make, particularly in the area of clinical trials. Patient groups will play a bigger role in

Aromatase inhibitors will become the standard adjuvant treatment for steroid-receptor-positive breast cancer

spreading information about ongoing trials, and we can also expect to see more patient advocates included in clinical trial committees, contributing their views and experiences to discussions and decisions about their design.

THE POLITICAL AGENDA

As of June 2003, Europe has been committed to a set of policies laid out in the Breast Cancer Resolution, which includes moving towards services provided through multidisciplinary teams in networks of specialist centres in line with the EUSOMA guidelines. Some progress can be expected on this front – faster in some countries than others. We can also hope to see progress in reaching the target set by the resolution of reducing breast cancer mortality by 25% and reducing disparities in five-year-survival across Europe from 16% to 5%.

THE MESSAGE

The health media will start to move away from the traditional emphasis on promoting breast awareness and breast checking – felt by most health commentators to be a 'completed job' – to translating and communicating to the public the ever-greater progress in breast cancer therapies.

The partnership between health professionals and health media can be extremely productive for all concerned – not least the patient. In the long run, the informed patient will raise standards of care. Traditional barriers between the medical profession and the media are breaking down and specialists are increasingly recognising the value of sharing their knowledge with the general public via the media.

GOOD FORTUNE AHEAD

Some bad omens were detected in some panelists' planetary divinations. There were warnings that bureaucracy will continue to impose an unnecessary impediment and complication on academic clinical trials, and that industry was generally unsupportive of academic clinical research. Bureaucracy on the part of funding agencies was also seen as a threat, as was the level of public funding for research, which was seen to be decreasing.

But looked at overall, the constellations concerning breast cancer seem to augur well for the coming year, predicting continuing progress on multiple fronts, improved working together, learning from each other, and ensuring that more patients than ever have access to top-quality services.

The main points made by the panellists will be distributed widely in the breast cancer community to help both inform their work and give an overview of where research, treatment, and care is headed in the coming months. "Some of these developments may seem like small steps, but they combine to produce improvements in care for patients and hope for those who treat them," said Alberto Costa, organiser of the Observatory. "It will be interesting to look back in five years time and see how things have changed."

THE PANEL

- Monica Castiglione-Gertsch – SAKK/IBCSG (Swiss Group Clinical Cancer Research/International Breast Cancer Study Group), Bern
- Alberto Costa – The European School of Oncology, Milan
- Nancy Davidson – Sidney Kimmel Comprehensive Cancer Centre, The John Hopkins University, Baltimore
- Richard Gelber – Dana Farber Cancer Institute, Boston
- Aron Goldhirsch – European Institute of Oncology, Milan
- Stella Kyriakides – Europa Donna/The European Breast Cancer Coalition
- Virgil Craig Jordan – Robert H Lurie Cancer Center, Northwestern University Medical School, Chicago
- Monica Morrow – Northwestern Memorial Hospital, Chicago
- David L Page – The Vanderbilt-Ingram Cancer Center, Nashville
- Gordon F Schwartz – The Breast Health Institute (founder), and Jefferson Medical College, Philadelphia
- Isla Whitcroft – Health Journalist, London

Locoregional techniques: under-rated and under-researched

Rob Stepney

Attempts to control or cure cancers using localised therapies are still in their infancy. Studies have been patchy and sporadic, with little attempt to collaborate across centres or across specialties. So a number of pioneers in the field got together to try to map out the next steps.

Where the problem caused by a tumour is primarily local, it would be logical to consider a local approach to treatment. Yet typically, locoregional approaches have been considered only as palliative treatments of last resort. When their use earlier in the course of disease has been advocated, there has often been more enthusiasm than effective evaluation. The numbers of patients studied has generally been small, collaboration limited, and results highly dependent on the expertise of the individual operator.

Nonetheless, there is a growing body of evidence regarding a variety of techniques used in different settings to show that, when used appropriately, locoregional techniques can have a significant impact not only on quality of life, but also survival. Experiences in advanced breast cancer, melanoma confined to a limb, soft tissue sarcoma, and isolated liver metastases from colorectal cancer have all shown that local tumour responses can be obtained with relatively low toxicity. The use of intra-arterial administration of chemotherapy may even open up treatment possibilities to patients who are too frail to tolerate systemic therapy. And this route could prove a highly cost-effective approach. Another big advantage is the possibility that patients with regionally advanced tumours of the limbs may be able to avoid amputation.

Despite this body of evidence, many of today's cancer patients are missing out because too many treatment centres remain unaware of the possibilities offered by current techniques, and too few studies are being done to improve locoregional treatments. So earlier this year, the European School of Oncology (ESO) brought together experts who have pioneered locoregional techniques in various cancers. They were asked to piece together an overview of the current state of knowledge and experience in this field, for dissemination among cancer clinicians, and with the aim of stimulating interest in carrying out trials.

A notable feature of the group was that both medical and surgical oncologists were well represented (see box overleaf for participants). This is important because the key to the successful use of locoregional techniques often lies with the way they are integrated within the wider therapeutic approach – with each other, with the best of systemic treatments, and with surgery – which requires collaboration between a variety of specialisms.

Options and evidence

The range of locoregional approaches (chemotherapeutic, biological and physical) is constantly expanding. The main ones can be listed as:

- Chemotherapy infused through the hepatic or internal mammary arteries
- Isolated limb perfusion with combinations of conventional cytotoxic agents and cytokines
- Chemoembolisation
- Embolisation utilising yttrium-labelled microspheres, which both mechanically obstruct the tumour vasculature and irradiate local malignant tissue
- Radiofrequency, laser and cryoablation
- Photodynamic therapy
- Hyperthermia

Though all of these have been used in various settings, only a few have so far been studied in randomised controlled trials. Maurizio Cantore reported a recent randomised, multicentre study into the effectiveness of intra-arterial administration of FLEC (5-FU, leucovorin, epirubicin and carboplatin) in patients with unresectable pancreatic cancer. The results showed that this locoregional therapy improved survival by an average of two months compared with patients treated with systemic gemcitabine.

Similarly encouraging results have come out of a randomised trial in colon cancer metastatic to the liver, which showed better survival when systemic chemotherapy was preceded by hepatic artery infusion than when systemic treatment was given alone. And, following promising phase II results, including a median 15 month survival, the European Organisation for Research and Treatment of Cancer (EORTC) has just accepted the protocol for a study of intra-arterial versus systemic fotemustine in ocular melanoma.

Primary and secondaries

Both locally advanced disease and metastases can be amenable to local therapy.

When surgery is not an option for hepatic metastases from colorectal cancer (CRC), lesions can still be treated – by cryosurgery, radiofrequency or laser ablation, or hepatic arterial infusion of chemotherapy. Phase I/II studies of intra-arterial irinotecan and oxaliplatin have achieved partial response rates of up to 40%. So it seems that newer drugs with good systemic efficacy are also active when locally administered, and their controlled evaluation is a clear priority.

Giammaria Fiorentini described how patients with unresectable chemotherapy-resistant CRC metastases can also be treated by hepatic artery administration of yttrium-90 labelled microspheres. This treatment has the potential to downstage disease to the point of resectability, as has been demonstrated by Andrew Kennedy and colleagues in the US. The beta-emitting isotope, carried by either resin or glass beads, irradiates malignant cells within a few millimetres of the site of embolisation, while delivering little radiation to normal liver.

A series of 243 patients treated this way have shown a median survival of 12.8 months. There were no deaths or cases of radiation hepatitis resulting from the treatment, and levels of pain, fever and gastrointestinal toxicity were considered 'reasonable'. Trials involving delivery of radioactive microspheres in combination with current chemotherapy are underway.

In locally advanced or recurrent breast cancer, good long-term local control is essential for quality of life, and taking a locoregional approach makes sense because of the strong correlation between dose and response seen with most cytotoxics. In Cantore's experience, the internal mammary artery is simple to cannulate. In locally advanced disease, infusion of FEM (5-FU, epirubicin and mitomycin) chemotherapy has achieved good rates of partial response, with the majority of tumours becoming operable, at the cost of mild systemic toxicity. But the intra-arterial approach is less effective with recurrent tumours.

Haematological toxicity was mild – with only one case of a grade 3 anaemia among 83 patients. Local erythema and hemialopecia were relatively common side effects

TASK FORCE MEMBERS

The Task Force on Locoregional Techniques met in Bentivoglio, Italy, and was hosted by the Ramazzini Foundation. The participating experts were, pictured from left to right *(opposite)*:

- Maurizio Cantore, Carrara, Italy – medical oncologist
- Martin Highley, Dundee, Scotland – medical oncologist
- Beniamino Palmieri, Scientific Co-ordinator of the Task Force, University of Modena and Reggio Emilia, Italy – surgeon
- Ferdy Lejeune, Lausanne, Switzerland – surgeon
- Giammaria Fiorentini, Empoli, Italy – medical oncologist
- Cornelis van de Velde, Leiden, the Netherlands – surgeon *(not shown)*
- Hans-Joachim Schmoll, Halle, Germany – medical oncologist *(not shown)*
- Morando Soffriti, Ramazzini Foundation – experimental oncologist *(not shown)*

The Task Force

and there were two cases of carotid spasm.

Whether used in locally advanced breast cancer or recurrent tumours, this locoregional technique, advises Cantore, should be undertaken only as part of an integrated strategy including systemic and surgical approaches.

Synergies

Martin Highley described how a temporary alteration in cell physiology caused by one drug may facilitate the uptake and cytotoxicity of another. For example, in isolated limb perfusion, combining tumour necrosis factor (TNF) with melphalan potentiates vascular changes, increases leakage of melphalan and leads to a six-fold higher concentration of the cytotoxic in tumour tissue. Combining agents that target the endothelial cell with agents that target the tumour cell may enhance the efficacy of treatment.

Combretastatin inhibits tubulin polymerisation in the endothelial cell, leading to destruction of neovasculature and necrosis in the tumour core. But combretastatin given alone leaves a viable rim, suggesting a role for chemotherapy. The optimal sequencing of vascular targeting agents and chemotherapy is not clear, but there is at least the potential for using the former to trap cytotoxic agents in the tumour.

Ferdy Lejeune and his Lausanne group have striking experience of how biological and cytotoxic agents can be combined within a locoregional approach. In patients with locally advanced melanoma of the limbs, isolated limb perfusion with melphalan achieves a 50–60% rate of complete response. Adding TNF and interferon gamma to the perfusion (accompanied by hyperthermia) raises the complete response rate to 80–90%, and disease can be confined to the limb for long periods. The superiority of intensive biochemotherapy over melphalan alone is supported by interim analysis of a phase III trial in the US.

The European TNF Core Group investigating this approach also has evidence of efficacy in 250 patients with inoperable soft tissue sarcomas. Isolated limb perfusion combining the three agents enabled amputation to be avoided in 80% of cases. Such perfusion exposes tumour to drug concentrations ten times greater than can be achieved with systemic administration. A corollary is that leakage into the systemic circulation must be kept below 10%, and continuously monitored.

One of the most intriguing examples of integrating locoregional approaches is hepatic arterial chemo-occlusion combining mitomycin and interferon alpha with microspheres. Both the microspheres and interferon are anti-angiogenic. This is an approach suited to the 30% of patients with metastatic CRC whose disease is confined to the liver for relatively long periods.

Hans-Joachim Schmoll and colleagues from Halle, Germany, have been treating patients with highly refractory disease with a three-weekly schedule. This is associated with low toxicity, requires a hospital stay of 2–3 days, and has induced disease stabilisation or better in 90% of cases.

On the basis of these promising results, there is a need for studies into the possible benefits of chemo-occlusion therapy in other cancers such as breast cancer, melanoma, leiomyosarcoma and neuroendocrine tumours, where the high vessel density in tumours such as carcinoid may justify intra-arterial treatment with anti-angiogenic agents like bevacizumab.

Other combinations of techniques discussed by the Task Force include the use of regional hyperthermia with neoadjuvant chemotherapy in the treatment of soft tissue sarcoma, for which promising results (49% five-

year survival) have been reported by Rolf Issels and colleagues. One possibility is that higher temperatures increase influx of cytotoxics into tumour cells.

Also mentioned were investigations being carried out in Slovenia, France and Sweden into the combination of chemotherapy (iv bleomycin and platinum) with the administration of electric shock to damage the tumour cell membrane – the technique of electrochemoporation.

And not forgetting surgery

Recognising the potential of the technologies considered above does not diminish the central role of surgery in locoregional disease control, and the importance of debate about how radical this should be. This is a particularly live issue in gastric cancer, where some practitioners favour extended lymph node dissection, while others argue for a more limited procedure.

Cornelis van de Velde presented the data of the Dutch Gastric Cancer Group, which had looked at comparative survival rates between patients treated using the conservative approach (D1) and those treated with the more radical approach (D2). At twelve years' follow-up there is still no survival advantage for patients randomised to the more extensive 'Japanese style' surgery. One reason is the greater mortality associated with radical surgery, arising mainly from postoperative complications following splenectomy and pancreatectomy. However, advances in surgical techniques mean that today this can largely be avoided. The outcome of any comparisaon between D1 and D2 procedures using current techniques might, therefore, be somewhat different.

Indeed, if mortality from postoperative complications is excluded from consideration, patients with more than three positive nodes appear to have experienced better survival when treated more radically. At ten years, the survival rate in the D2 group was 26%, while it was 0% among D1 patients. Among gastric cancer patients with only one positive node, there was no significant survival difference. A study comparing good, extensive surgery with locoregional control versus US-style postoperative chemoradiotherapy is now planned.

The next steps

The meeting of the Task Force revealed that a wide range of techniques are being tried out in many settings either to avoid the toxicity of systemic therapies or to add to their impact. Side-effects generally appear to be less unpleasant and dangerous than with many systemic treatments, though care is needed to ensure that where high concentrations of toxic drugs are used, they do not leak out into the general circulation.

The problem remains a shortage of randomised controlled trials that can provide the level of evidence needed to demonstrate which techniques or combinations of techniques give the best results in which settings. Currently, there are not even any agreed criteria for evaluating the effects of such treatments.

The Task Force agreed a number of priorities to speed up progress in this area:

- Establish evaluation criteria for trials of locoregional therapy
- Encourage collaboration within and across disciplines. The Italian co-operative group SITILO (Societa Italiana di Terapie Integrate Locoregionali in Oncologia) may serve as a model
- Examine lohether cytotoxics such as irinotecan and oxaliplatin show efficacy when given intra-arterially
- Explore multimodality approaches. In several tumours, chemoradiotherapy has become the norm. Techniques should be tried in combination – optimal systemic chemotherapy with optimal local chemotherapy, or systemic chemotherapy with radiofrequency approaches or hyperthermia, for example
- Evaluate new ways of quickly establishing whether treatment is having an effect. Functional Positron Emission Tomography (PET), nuclear magnetic resonance (NMR), ultrasound and tumour markers may all usefully complement conventional evaluation of effect.

An ESO course on Locoregional Control of Advanced Cancer is scheduled for 12-13 September 2005, in Orta, Italy.

ESO TASK FORCES

Since 1993 ESO has been bringing together small groups of experts to address important issues in oncology. These Task Forces have covered topics ranging from gene therapy to nutrition in the cancer patient. The meetings' conclusions are generally published in the ESO series of *Task Force Reviews* and may appear as position papers, usually in the *European Journal of Cancer*. Where appropriate, Task Forces lay the groundwork for ESO's educational activities.

Europe set to act over paediatric drugs

Mary Rice

Child cancer patients are routinely given drugs that have only ever been tested in adults. But developers may soon find themselves forced to extend trials to paediatric populations if they want new drugs approved in Europe.

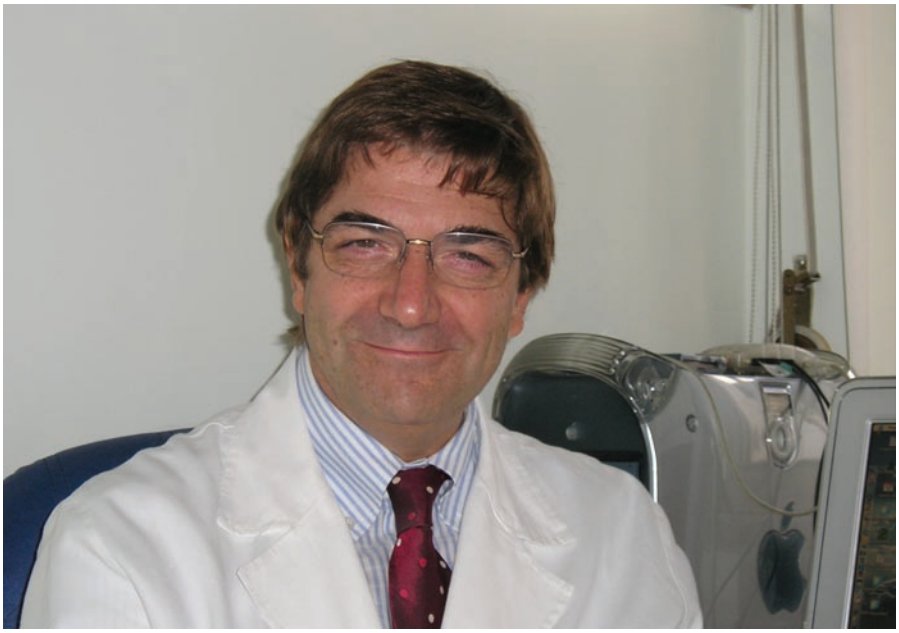
After a lengthy consultation process, at the end of September the European Commission (EC) finally published a regulation (draft legislation) aimed at tightening up marketing authorisation for paediatric medicines. The proposal follows a request from Member States to find ways to increase the number of drugs intended for use in children.

Pharmaceutical companies are reluctant to support studies to evaluate new drugs in children because the market is limited and the high costs cannot always be recouped by sales. There is also the problem of finding enough participants to have sufficient statistical power to detect small treatment effects that might be significant. Add to this the particular ethical and legal challenges involved – What constitutes an acceptable risk for a child participating in research? – and it becomes easy to see why paediatric drug research is so limited. "There needs to be a proper balance between the potential benefits and a reasonable expectation of safety," says Dr Riccardo Riccardi, Director of the Paediatric Oncology Division of the Catholic University of Rome, who is involved in international studies of new agents in paediatric oncology. "In children with cancer, clinical trials should start only after an adult phase I study has been completed and reasonable information on potential toxicity has been collected."

Consent issues are complicated too. In paediatric trials, consent is obtained by proxy from the child's parents or guardian. "Most parents, at least in Italy, are avidly seeking experimental treatments when standard therapy fails. Only a few are more reluctant to submit their child to an experimental drug or procedure than they would be if asked for their own participation. The term 'permission' rather than 'consent' may be used for parents making a decision for their child," says Riccardi.

Nearly a quarter of the EU's 480 million citizens are below 19 years of age. Yet over 50% of medicines given to children, including the newborn, have never been tested for their effects in this group. This means that the health of children may suffer, as doctors cannot be sure of the effectiveness of many medicines, nor do they know what dose is appropriate or exactly what the side-effects may be. The EC's initiative is aimed at promoting the development of badly needed paediatric drugs while ensuring that the research needed for authorisation is of the highest quality. The legislation, which has yet to pass through the Parliament and the Council of Ministers, would require pharmaceutical companies to present the results of trials involving children when requesting authorisation for new products. The effects on children would therefore be displayed on the label, and the same procedure would apply to drugs already on the market should the company wish to extend use to children. But the European legislative process is long and it seems unlikely that these measures will come into effect before 2007 at the earliest.

In exchange for the extra costs involved, companies would be given a six-month patent extension. "The paediatric exclusivity legislation introduced by the FDA in 1997, which also gives a six-month extension, has been a great success in the US and led to a considerable increase in the number of drugs available for paediatric use. I think that such an incentive would dramatically improve the situation in Europe," says Riccardi. More than 60 labels with new paediatric information for estab-



Riccardo Riccardi

lished drugs have been created in the US since the six-month extension came into force.

Statistics show that cancer is the leading cause of death in children, outside of accidents. In Europe each year about 13,000 children will develop cancer and 3,000 will die of it, yet these children's access to innovative therapy is extremely limited. From 1995 to 2002, only 2 of the 25 new drugs approved for marketing authorisation by the European Medicines Agency (EMEA) for cancer treatment were submitted with paediatric data.

"Our goal as paediatric oncologists," says Riccardi, "is to offer to European children struck by cancer newer, better, and safer compounds. Any new regulation should cover the way clinical studies are conducted in order to obtain meaningful data with maximum safety. The process should include, for example, the development of specific paediatric formulations such as the development of compounds that can be administered as a syrup."

The proposed regulation covers a number of issues, in addition to the six-month patent extension and the requirement to present paediatric trial data when applying for authorisation:

- A new expert committee will be established within EMEA to assess and agree trial design
- A new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), will be set up for off-patent medicinal products developed specifically for paediatric use
- Safer medicines and compulsory submission by the industry of existing studies in children will be required
- An EU inventory of the therapeutic needs of children and an EU network of investigators and trial centres will be set up to conduct the studies required
- Free scientific advice for the pharmaceutical industry will be provided by EMEA.

The EC proposals were subjected to an extended impact assessment carried out by external contractors and designed to estimate the economic, social and environmental impacts of the initiative. The report of the assessment found that the regulation should lead to the improvement of the health of European children through ensuring the availability of evidence-based information on paediatric medicines and hence the greater availability of authorised medicines for children.

The report found that, overall, the costs of clinical trials in children would add less than 0.5% to the costs of developing the medicines, which would be more than compensated for by the economic advantages of the six-month extension to patent protection.

"The establishment of a paediatric committee is in itself a step towards fulfilling paediatric needs as far as new medicines are concerned," says Riccardi. "The committee would be able to identify the most important needs of children and will have specific knowledge that will help to prioritise the drugs to be studied."

He warns, however, that while these changes are badly needed and their adoption should improve the present situation, EMEA is not equivalent to the FDA, and it may be more difficult to reach consensus among EU member states on specific aspects, mainly relating to existing national rules or funding. "Vigilance is called for," he concluded, "in order to ensure that the health of Europe's children does not suffer as the result of political infighting."

Sharing secrets with the FDA

Kathy Redmond

EMEA (the European Medicines Agency) and the FDA (the US Food and Drug Administration) have published a plan for implementing confidentiality arrangements agreed in principle last September. The purpose of the confidentiality agreement is to allow the regulatory agencies to share expertise, perspectives and ideas for alternative approaches to regulation. It covers both regular and ad hoc exchange of information, including information on pre-authorisation and post-authorisation applications, inspections and guidance documents, and applies to all products that fall within the remit of the EMEA and FDA.

A key part of the implementation plan is a pilot programme for companies to obtain parallel scientific advice from the two agencies, which should result in patients getting faster access to new medicines, with a particular emphasis on important breakthrough drugs. Mechanisms have been put in place for EMEA, FDA and pharmaceutical companies to exchange views on scientific issues during the development phase of new medicinal products. An exchange programme for staff of both agencies is also foreseen.

The newly published plan details the information and documents the two agencies will exchange and the process for monitoring the implementation of the confidentiality arrangements.

In a separate bid to help streamline and simplify regulatory procedures, EMEA has set up a new Committee on Herbal Medicinal Products (HMPC). The move comes in response to the Directive on Traditional Herbal Medicinal Products that came into force earlier this year. The new provisions bring in a much simpler registration procedure for herbal medicinal products, which should help harmonise the procedures and provisions concerning these products across Europe.

Genetic testing

EMEA has also starting fulfilling its newly adopted role of providing tailor-made information to patients, with a leaflet aimed at patients participating in a clinical trial that involves pharmacogenetic testing. Under the slightly obscure title of "Understanding the terminology used in pharmacogenetics", the leaflet provides patients with vital information about the risks to privacy inherent in such trials together with advice about how patients can protect their identity and safeguard their genetic information. Copies of the leaflet are available from the EMEA site: www.emea.eu.int.

SCIENCE PHOTO LIBRARY / GRAZIA NERI

The difficult ethical, social and legal issues in human genetic testing in research and healthcare applications were also the focus of a European citizens' and stakeholders' conference convened earlier this year by the European Commission. The conference was based on a report and 25 recommendations prepared by a high-level, independent Expert Group. A report on the stakeholder conference is due shortly, but in the meantime, interested parties are invited to contribute to a debate on the 25 recommendations via a forum on the EC website: *http://europa.eu.int/comm/research/conferences/2004/genetic/index_en.htm*

ELI LILLY'S ALIMTA (pemetrexed) has been granted marketing authorisation by the European Commission for use, in combination with cisplatin, in patients diagnosed with malignant pleural mesothelioma, and, as a single agent, as second-line treatment for patients suffering from non-small-cell lung cancer.

■ ■ ■

DRUG REGULATORS IN SEVERAL EUROPEAN countries including Germany, Sweden, Denmark, Finland, Belgium, Hungary, Portugal, and Romania have approved the extension of another Lilly product – Gemzar (gemcitabine) – for the treatment of recurrent epithelial ovarian cancer. Gemzar is already approved for the treatment of patients with pancreatic, non-small-cell lung, metastatic breast and bladder cancers.

■ ■ ■

EUROPEAN AUTHORITIES HAVE AGREED to extend the indication for Roche's MabThera (rituximab) to first-line use in treatment of indolent non-Hodgkin's lymphoma in combination with conventional chemotherapy. The EC has also approved an extension to the dosing interval for Amgen's anti-anaemia product Aranesp (darbepoetin alfa), which can now be given once-every-three-weeks in the treatment of anaemia in adult cancer patients with non-myeloid malignancies who are receiving chemotherapy.

■ ■ ■

SWISSMEDIC, THE SWISS DRUG REGULATOR, has approved Femara (letrozole) for the extended adjuvant treatment of postmenopausal women with hormone receptor positive or unknown early breast cancer who have received post-surgery tamoxifen therapy for five years. Switzerland is the first European country to have approved the extended adjuvant indication.

■ ■ ■

THE MARKETING AUTHORISATION for Guilford Pharmaceuticals' GLIADEL(R) Wafer (polifeprosan 20 with carmustine implant) has been extended to use in newly-diagnosed patients with high-grade malignant glioma as an adjunct to surgery and radiation. GLIADEL(R) was previously authorised for use only in recurrent surgery for glioblastoma multiforme.

■ ■ ■

BIOENVISION HAS SUBMITTED an application for marketing authorisation to EMEA for clofarabine for use in refractory or relapsed acute leukaemias in children.

■ ■ ■

ROCHE HAS SUBMITTED A MARKETING authorisation application to EMEA for Tarceva (erlotinib) for the treatment of advanced non-small-cell lung cancer. A similar application has been filed with the FDA. The company has also applied to EMEA for an extension of the indication of Xeloda (capecitabine) to the adjuvant treatment of colon cancer.

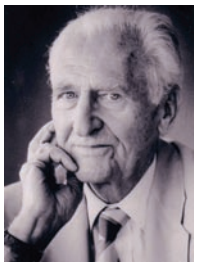
■ ■ ■

THE MERGER BETWEEN SANOFI AND AVENTIS has resulted in the birth of Sanofi-Aventis, the world's third largest pharmaceutical company. Oncology operations got off to a good start – the European authorities extended Eloxatin's (oxaliplatin's) indication to cover the adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour and Taxotere's (docetaxel's) to cover hormone-refractory prostate cancer.

NEW ORPHAN DRUGS

A number of agents with cancer indications have been designated as Orphan Medicinal Products by the European Commission. They include:

- (R,S)-3-(bromomethyl)-3-butanol-1-yl-disphosphate (Innate Pharma) for the treatment of renal cell cancer
- Porfimer sodium used with photodynamic therapy (Axcan Pharma International) for the treatment of cholangiocarcinoma
- Midostaurin (Novartis Europharm) for the treatment of acute myeloid leukaemia
- Sorafenib tosylate (Bayer Healthcare) for the treatment of renal cell carcinoma
- Anti epidermal growth factor receptor antibody h-R3 (Oncoscience) for the treatment of glioma
- 5,10-methylene-tetrahydrofolic acid (Interface International Consultancy) for the treatment of pancreatic cancer in combination with 5-fluorouracil
- Homoharringtonine (Stragen France) for the treatment of chronic myeloid leukaemia
- Recombinant human interleukin-21 (Novo Nordisk) for the treatment of renal cell cancer



Richard Doll: Science will always win in the end

➜ Interview by Anna Wagstaff

In 1950, Richard Doll showed the world that smoking causes lung cancer. Today, aged 92, a word from him can still cause anxiety in the Nokia boardroom or have us counting our portions of fruit and veg. He carries the responsibility lightly, because he believes in the power of evidence. After all, when it comes to the causality of cancer, he wrote the rules.

Lung cancer had been rising sharply for decades before your groundbreaking report showed, with only a one in a million scintilla of doubt, that smoking is a cause of lung cancer. Why did such a strong association take so long to identify?

RICHARD DOLL Cigarette smoke had first been suspected in the 1920s, but some pathologists tried to produce skin cancer in mice by smearing them with cigarette smoke tar. When there was no response, smoking was ruled out as a possible carcinogen, and researchers turned their attention to other possible causes.

The technique of testing for carcinogens by exposing animals to them had only been introduced in about 1919, in Japan, and for the next two or three decades, scientists thought that's the way we discover the causes of cancers, by getting suspect materials and putting them on the skin of mice.

I myself did not expect to find smoking was a major problem. If I'd had to bet money at that time, I would have put it on something to do with the roads and motorcars.

Was yours the first epidemiological study on lung cancer?

RICHARD DOLL There were a few others, but we were the first to have sufficient confidence in our findings to state that "We conclude that smoking is a cause and an important cause of the disease."

A couple of very primitive studies had been carried out in Germany, but they were very flawed. For example, one used the average age of lung cancer patients as a basis for selecting control patients – so if the average age of the lung cancer patients was 54, they interviewed a lot of people aged 54. You really need to have the separate experiences of a 70-year-old and a 30-year-old, you can't assume that the experience of a 54-year-old is representative.

Then there was a US study that came out about the same time as ours and had similar findings, but because they had used less rigorous techniques, they were more cautious about drawing conclusions from their data, and merely concluded that there was an association they'd found which might imply causality.

With Richard Peto, who became known in the cancer world as the man behind the Oxford Early Breast Cancer Collaborative Group, which first proved the benefits of adjuvant therapy. Doll brought Peto with him to Oxford when he took up his post as Regius Professor of Medicine at the University in 1969

I did not expect to find smoking was a major problem… I would have bet on roads and motorcars

The trouble was that, until then, epidemiology had been concerned almost entirely with infectious diseases, which required very different methods and tended to look at differences between entire populations – differences in rainfall, temperature, things like that. With cancer and chronic diseases, you need to compare individuals with the disease against those without. There are all sorts of biases that can affect this kind of epidemiological study, and that was not understood at the time. A person being interviewed, for instance, will tend to overemphasise something that they think might be useful. It took some time to establish and find techniques to eliminate all the biases that can affect the results.

We were confident of our data because we had taken steps to ensure that our results were robust. Chance you could cut out immediately, because you were talking about odds of less than one in a million of getting our results by chance. Then you had to show that your results weren't biased, and then you had to show that the results were not due to what is now called confounding; that it was not smoking that caused the disease, but smoking was associated with something else that did. For example lung cancer is associated with drinking alcohol – smokers tend to drink more alcohol.

Then we checked our results against ecological evidence, to see what sense it made in the world at large. If smoking is the cause, we ought to find that wherever the disease was common, smoking should be common, and vice versa. So where people didn't smoke there shouldn't be much lung cancer. And that's what we found when we looked round the world.

Was the medical world convinced?

RICHARD DOLL Not at all. Sir Harold Himsworth, the Secretary of the Medical Research Council (MRC), who had commissioned the study, accepted the results straight off. But most cancer research workers did not accept it, and in fact they advised the Department of Health that they shouldn't take any action because they were uncertain about what it meant.

It wasn't until 1957, when the Government asked the MRC for a formal opinion as to whether our conclusion was correct or not, that the MRC formally considered it and said it was correct and advised the Government to that effect. The result was that the Minister of Health in 1957 called a press conference to announce the results of the MRC consultation. He announced that the MRC had advised them that smoking was the cause of the great increase in lung cancer. While he was reporting this to the media, he was smoking a cigarette himself!

One of the problems we found in trying to convince the scientific community was that thinking at that time was dominated by the discovery of bacteria such as diphtheria, typhoid, and the tubercle, which had been the basis for the big advances in medicine in the last decades of the 19th century.

When it came to drawing conclusions from an epidemiology study, scientists tended to use

While the minister announced that smoking caused lung cancer, he was smoking himself

the rules that had been used to show that a particular germ was the cause of an infectious disease – Koch's three postulates. Koch was a great German pathologist who discovered the tubercle bacillus, and one of his postulates was that you must always find the organism in every case of the disease.

When we did our study on lung cancer and smoking, 50 years later, a number of scientists thought this applied to the cause of chronic diseases. A lot of people said, "Smoking can't be the cause of lung cancer because I have seen a case in a non-smoker, and therefore by Koch's postulate smoking is not the cause."

But, of course, nobody was saying it was *the* cause; what we were saying is that it is *a* cause. People didn't realise that these chronic diseases could have multiple causes. And smoking is only one cause of lung cancer – it happens to be much the most important cause, however.

How did you convince the doubters?

RICHARD DOLL When we saw that, apart from Sir Harold Himsworth and one or two others, practically no-one believed our conclusions, we thought it's no good repeating the study. So we designed another one, using a different method. We decided to look at people's smoking habits and see whether that could predict who would contract lung cancer.

We chose doctors as our sample, principally because they were easy to follow up, and we planned to do the study for five years. But within two and a half years, we already had 37 deaths from lung cancer – none in non-smokers, and a high incidence in heavy smokers. The association was very clear. It turned out to have been very fortunate to have chosen doctors, from a number of points of view. One was that the medical profession in this country became convinced of the findings quicker than anywhere else. They said, "Goodness! Smoking kills doctors, it must be very serious," and, of course, a very high proportion gave up.

After five years we had around 70 cases, but by this time, our results were beginning to show that smoking was also associated with a number of other diseases, particularly with heart disease, so we decided to continue the study, though this had never been the initial plan.

Your findings have implications for us all. Do you get drawn in to discussions about people's lifestyles?

RICHARD DOLL My job has been to try to find out what the causes are, or what is the efficient treatment. If I then go round telling people what they should do, I may get prejudiced because I'm committed to a particular opinion, and as a scientist you must always be prepared to change your mind if the evidence changes.

I am now committed to the viewpoint that people shouldn't smoke, but that's 50 years after the first observation. I never gave any advice for the first 30 years. But it is so established now that there is no question of my being prejudiced.

People can also over-react. Radiation is an example – people are ridiculously frightened of

They said: Goodness! Smoking kills doctors, it must be very serious

Tobacco bosses in 1950 were horrified by the idea that what they were selling was killing people

it. I also think we've gone too far in eliminating asbestos – I mean the less dangerous white type, which carefully handled probably does more good than harm. Several hundred British sailors died in the Falklands War who needn't have, because they hadn't got the adequate fire control that you had with asbestos.

Fifty years ago you showed the world that smoking can kill. Why do you think so many youngsters are still not getting the message?

RICHARD DOLL Young people will always behave a bit recklessly. That's why it's so important that we now can show that giving up smoking early in life is really effective. I think we're going to save more lives by persuading people to give up than we are by stopping people from starting.

Obviously you try to educate children and young people, but you know you are not going to win with all of them. Even my own children smoked. My son smoked from about age 12 to 16. My daughter didn't stop till she was 30.

Did you personally come up against the tobacco industry?

RICHARD DOLL What you've got to remember is that the directors of the tobacco companies in 1950 were responsible people, insofar as the directors of any firm were, and they were horrified by the idea that what they were selling was killing people. They made serious efforts, perfectly reasonably, to disprove the claim, but their own statistical advisor after a few years told them that it was a waste of time and that he was convinced that smoking caused lung cancer.

I remember he rang me up and said that he agreed with my findings and that he was going to have to leave his job.

He wanted to take the opportunity of his final two weeks' of expenses allowance to invite me and my wife out to dinner. As it happened, his employers accepted his advice, and he agreed to continue working for them on the basis that they would never publicly deny that smoking caused lung cancer.

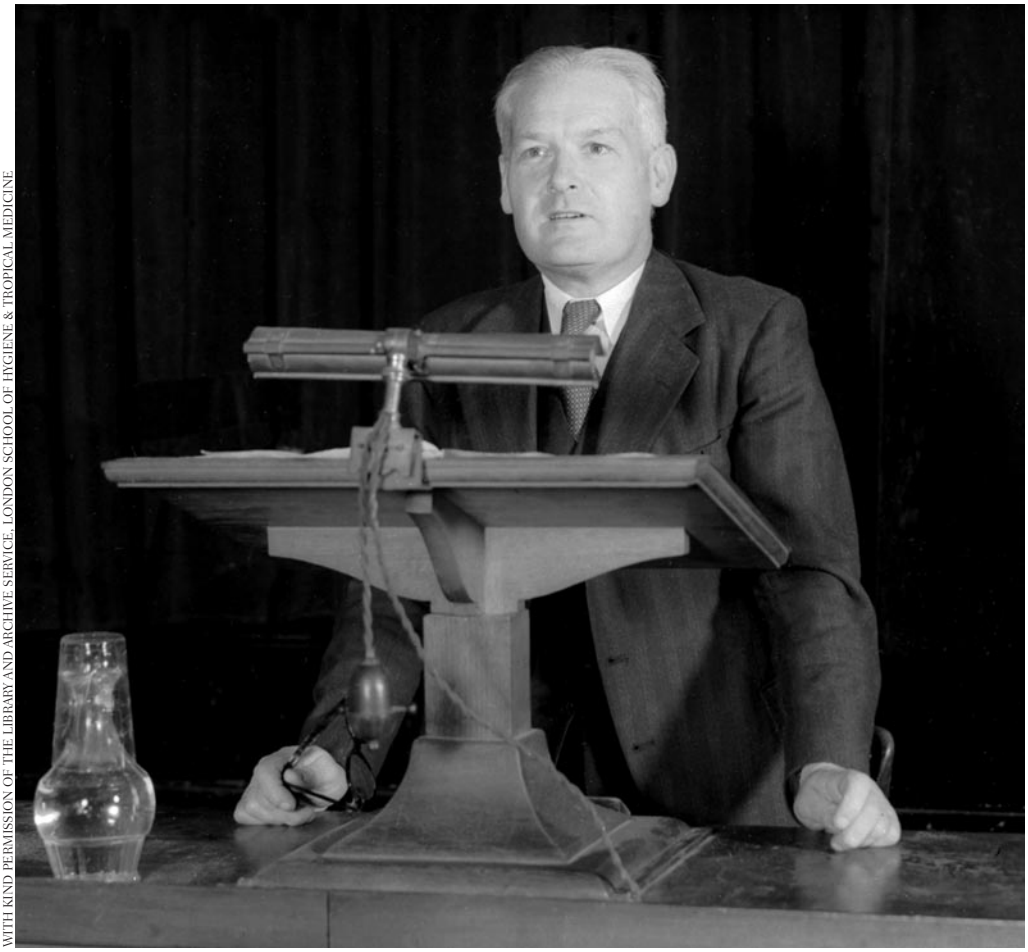
It's a different case with today's directors of the tobacco industry. They have gone into it knowing perfectly well that they are selling something that is a lethal material, and they are to my mind thoroughly immoral people. But that wasn't true of the directors of 1950.

The tobacco industry in America did not react at all in the same way, and they tried to get a colleague of mine, Ernest Wynder, sacked from his job with the Sloan-Kettering. They put pressure on the Director not to allow Wynder to publish anything that claimed smoking caused disease, and the Director did try to suppress his studies. Wynder, however, responded by setting up his own organisation and getting support from somebody else to carry on doing the research. So when he published his results, they didn't have the Sloan-Kettering stamp. Sloan-Kettering came out of it very badly.

However, despite this sort of pressure, the leading epidemiologists in America all got together fairly early on – in the late 1950s – and said they regarded it as proved that smoking causes disease. The trouble was the American law courts. The industry made it so expensive to sue them that it wasn't for some years that you got very wealthy groups of lawyers who were prepared to take them on. The industry could make it so expensive by raising objections and making it last a very long time.

Did you feel a sense of triumph when the courts finally found against the mighty tobacco industry?

RICHARD DOLL Science will always win in the end.



Sir Austin Bradford Hill – grandfather of modern epidemiology and Richard Doll's boss and teacher. As Professor of Medical Statistics at the London School of Hygiene & Tropical Medicine, he was the man the Medical Research Council turned to as the death toll from lung cancer rose ever higher. Together, he and Doll worked out the techniques that fingered smoking as the culprit. Bradford Hill wanted to be a doctor, but World War I ended his hopes and would probably have ended his life, had his service as a fighter pilot not been cut short when he contracted tuberculosis. He pulled through, but it was too late to start a medical career, so he went into statistics and applied it to medicine. The rest is history

What we're left with now are the smaller risk factors such as alcohol for breast cancer

Your discovery that smoking causes lung cancer was the preventive equivalent of the 'magic bullet'. Are there any more major factors that we don't yet know about?

RICHARD DOLL No there are not. We've eliminated so many causes of cancer. What people don't realise now is how many occupational cancers there used to be. They've all been cleared up. 2-naphthylamine, for instance, which was used in dyes and in the preparation of rubber, led to a very high incidence of bladder cancer among those who worked with it. That's gone. Road workers would get skin cancer from tar, or lung cancer from the fumes. Many oils used for lubricating machinery would result in skin cancer or cancer of the scrotum. Asbestos. All these work-related cancers have now been eliminated. We've also made huge strides identifying which cancers have an infectious origin. We now know,

Tamoxifen, for instance, was not being used in this country until Peto's collaborative analysis in 1988

for instance, that cervical cancer has a viral origin, and we shall have a vaccine against it in a few years' time. We are beginning to find other cancers with viral origins. Hepatitis B and C are major causes of liver cancer in many parts of the world, the Epstein Barr virus causes some rare cancers in the Far East, but is also responsible for some cases of Hodgkin's disease. And we now know that gastric cancer, which dropped dramatically in incidence during the last century, is largely caused by the helicobacter pylori bacterium. What we're left with now are the smaller risk factors, such as alcohol for breast cancer, which can only be detected by collaborative studies looking at populations of tens of thousands rather than the hundreds that we used to use. This sort of work has been pioneered by Richard Peto, whom I brought with me from London when I took up my position of Regius Professor at Oxford University. This has to my mind been his really major contribution. These large-scale studies were undreamed of until he demonstrated the possibility by collaborating with different people in different countries.

The increased effectiveness of new treatments can also be too small to measure except through this sort of study. Tamoxifen, for instance, was not being used in this country until Peto's collaborative analysis in 1988. The evidence was all there but it was in little bits and contradictory. It wasn't until the evidence was all put together that you could say "Look! It's absolutely clear that giving women tamoxifen after the operation reduces their mortality by about 10–15%. You saw a very clear answer, and people changed their habits overnight. Very few people had been using it, or they had only been using it for a year. After this study everyone started using it and they realised they had to continue using it for up to five years.

What do you see as your legacy to the world of epidemiology?

RICHARD DOLL Sir Austin Bradford Hill has largely been forgotten about nowadays because he is dead. But he was my boss and my teacher, and the methods and techniques we developed together in order to find out why lung cancer was increasing so dramatically are still used to this day.

Bradford Hill later codified these into what he termed "nine guidelines", (often wrongly referred to as "criteria") which are universally accepted now. They are cited in courts of law.

I wrote an article about three years ago on proof of causality – proof that something is actually a cause of a disease – which made use of what I'd learnt from Bradford Hill, and which is now used as a reference point for epidemiologists.

And of course our report that established smoking as an important cause of lung cancer was very important. That was the first serious epidemiological study ever done into cancer, at a time when there were probably no more than a dozen of us working on this issue worldwide. Looking back with the benefit of more than 50 years' hindsight, I can honestly say that we did a good job.

Looking back with more than 50 years' hindsight, I can honestly say: we did a good job

Treatment of metastatic CRC takes two steps forward

Janet Fricker

The US approval of cetuximab and bevacizumab for patients with metastatic colorectal cancer is seen as the dawn of a new era in targeted therapies. Used together with cytotoxic regimens, they can add months to a patient's life – but they don't come cheap.

In early 2004, the FDA (the US drugs regulator) approved two monoclonal antibodies, cetuximab (Erbitux) and bevacizumab (Avastin), for patients with metastatic colorectal cancer (CRC). Trials show that the two drugs, used in conjunction with cytotoxic regimens, produce encouraging extensions of median survival, stabilise tumours and provide welcome further therapeutic options in a group of patients where treatments have been limited.

Statistics show that CRC – which includes cancer of the colon, rectum, anus and appendix – is now the most common site of human non-skin cancers in Europe. In 2000, 304,687 new cases of CRC were diagnosed in Europe, compared to 301,090 cases of lung cancer. In the same year there were 167,184 deaths from CRC in Europe.

Age-specific incidence and mortality rates show that most cases of CRC are diagnosed after 50 years of age. Genetic, experimental, and epidemiological studies suggest that colorectal cancer results from complex interactions between inherited susceptibility, environmental causes and lifestyle factors. Groups with a high incidence of CRC include those with hereditary conditions, such as familial adenomatous polyposis and hereditary non-polyposis colorectal cancer, which together account for around 6% of cases.

Metastatic disease is widespread, with around 30% of CRC patients presenting with advanced disease. One of the main reasons for late diagnosis is that people hide symptoms. A recent survey of 21,000 Europeans by the United European Gastric Federation revealed that 66% of all respondents regarded embarrassment as a barrier to seeking early diagnosis for CRC. Overall, the five-year case-fatality rate is 50%, but for localised disease the five-year survival rate approaches 90% for cancer of the colon and 80% for cancer of the rectum.

In patients with metastatic CRC, chemotherapy has been effective in prolonging survival and time to disease progression. Without chemotherapy, the median duration of survival among patients with metastatic CRC was eight months. With the introduction of fluorouracil, it increased to 12 months. Then, over the last five years, availability of other cytotoxic agents (capecitabine, irinotecan and oxaliplatin) further extended median survival to 21 months. But once these three standard drugs had failed, there were no further treatment options. Now it is anticipated that the use of cetuximab and bevacizumab will have an additional impact on survival.

Cetuximab

On 12 February 2004, the FDA approved cetuximab under its accelerated approval programme as an intravenous combination treatment with irinotecan for the treatment of patients with metastatic CRC, or for use alone if patients cannot tolerate irinotecan. Approval in Europe followed in June.

Cetuximab, is a monoclonal antibody against the epidermal growth factor receptor (EGFR) which, when activated, contributes to cellular proliferation, migration, angiogenesis and apoptosis, all of which become deregulated in cancer cells. EGFR is of particular relevance in CRC, since expression or up-regulation of the EGF-receptor occurs in 60–80% of cases. In addition, expression of the

receptor is known to be associated with poor survival.

Approval of cetuximab was largely based on the findings of the bowel oncology with cetuximab antibody (BOND) study, published recently in the *New England Journal of Medicine* (vol. 351, pp 337–345). In the study, 329 patients with EGFR-expressing metastatic CRC, whose disease had progressed after receiving irinotecan, were randomised in a 2:1 fashion to receive the combination of cetuximab and irinotecan or cetuximab monotherapy.

Results showed the response rate for the 218 patients receiving combination therapy was 22.9%, compared to 10.8% for the 111 patients receiving monotherapy (p=0.007). The median time to progression was 4.1 months for the combination therapy group compared to 1.5 months for the monotherapy group (p<0.001), and median survival was 8.6 months for the combination therapy group, compared to 6.9 months in the monotherapy group (p=0.48). "The combination therapy group had a significantly higher response rate and a significantly longer time to progression than the monotherapy group, suggesting that the combination of irinotecan and cetuximab should be preferred for patients with irinotecan refractory cancer," write the authors.

The effectiveness of combination therapy suggests that cetuximab may work by circumventing irinotecan resistance. The authors hypothesise that EGFR inhibition by cetuximab may overcome resistance by abrogating drug efflux, restoring apoptosis or impairing DNA-repair activity.

Eric van Cutsem: concerns over drug costs must not get in the way of significant advances in biomedical research

Roberto Labianca: approval of bevacizumab is significant as this is the first angiogenesis inhibitor shown to be efficacious in human cancer

"There was a wide variety of response. In some patients we could control the cancer for one or two years, while in others we couldn't achieve anything," said Eric Van Cutsem, one of the lead researchers in the study, and chairman of the EORTC Gastrointestinal Tract Cancer Group.

The study was not, he added, designed to show an effect on overall survival. This will be explored in the new trials currently underway in patients with metastatic disease who have not received previous treatment. Here, patients are being randomised to receive standard chemotherapy or standard chemotherapy plus cetuximab – a design considered comparable to the bevacizumab study (see below).

Bevacizumab

On 26 February 2004 the FDA approved bevacizumab as a first-line treatment for patients with metastatic CRC. The drug was approved for use in combination with intravenous 5-fluorouracil-based chemotherapy for treatment of people diagnosed with metastatic CRC for the first time.

"The approval of bevacizumab is of particular note since it's the first time that an angiogenesis inhibitor has been shown to be efficacious in human cancer," said Roberto Labianca, director of the Oncology Department of Ospedalia Riuniti and president of AIOM, the Italian medical oncology society. At the end of October, bevacizumab was given a positive opinion by the Committee for Human Medicinal Products (CHMP), and it is now awaiting full approval by the EC.

"With an average survival gain of five months, a fraction of patients will live a lot longer"

"The implications of these two studies are great for the management of advanced CRC"

In their phase III trial assessing bevacizumab (*N Engl J Med* 2004; 350:2335–2342), Herbert Hurwitz and colleagues, from Duke University Medical Center, Durham, US, randomly assigned 813 patients with previously untreated metastatic colorectal cancer to one of two groups. The first group received IFL (the addition of irinotecan to the fluorouracil and leucovorin systemic treatment, also known as the Saltz regimen) plus bevacizumab, while the second received IFL plus placebo.

Results showed that the median overall survival for patients who received IFL plus bevacizumab was 20.3 months compared to a median overall survival of 15.6 months for those who received just IFL ($p<0.001$). "The increase of 4.7 months in the median duration of survival attributable to bevacizumab is as large or larger than that observed in any other phase III trial for the treatment of colorectal cancer," wrote the authors. In addition, the median progression-free survival increased from 6.2 months to 10.6 months ($p<0.001$) for patients given bevacizumab, and the objective response rate was 44.8% versus 34.8% ($p=0.004$).

Labianca commented: "I think that the gain of five months in overall survival obtained by bevacizumab is important, because it means that a fraction of the patients will achieve much longer survival or might even be cured. It suggests that in the adjuvant setting we have the potential to cure many patients." Van Cutsem added that another way of presenting these results, which might have demonstrated greater advantage for the bevacizumab combined treatment, would be to look at the number of patients alive at two years and compare this to controls.

Two steps forward

Commenting on both sets of findings, Van Cutsem said: "Taken together, the implications of these two studies are great for the management of advanced colorectal cancer. Here are two drugs that are well tolerated, that can either prolong life or stabilise tumours so that patients achieve a better quality of life."

He adds that criticisms levelled at the targeted therapies that they do not affect cure rates are premature, since, to show an effect on cure rates, trials are needed in the adjuvant setting. "For both cetuximab and bevacizumab trials are now planned where patients will undergo surgical resection and then be randomised to receive standard chemotherapy or chemotherapy plus the addition of cetuximab or bevacizumab (adjuvant setting). This will show whether the agents can decrease the chance of recurrence," said Van Cutsem. But the financial costs of these new treatments is an issue. In an accompanying editorial to the cetuximab study (*N Engl J Med* 2004; 351:317–319), Deborah Schrag, from the Memorial Sloan-Kettering Cancer Center, New York, estimates that the addition of monoclonal-antibody therapy to the eight-week course of initial treatment for the 56,000 patients in the US

David Cunningham: challenge for the future is to define the populations who are most likely to benefit from the new therapies

Mike Keighley: introduction of widespread screening programmes would deliver a far greater impact on overall survival

who receive a diagnosis of stage IV CRC and recurrent metastatic disease each year, would cost $1.2 billion (961,000 euros). She adds that these costs are exclusively for drugs and do not include the costs of preparation, administration and supervision or supportive medications.

Robert J Mayer, from the Dana-Farber Cancer Institute, Boston, estimated in an accompanying editorial to the bevacizumab study (*N Engl J Med* 2004; 350:2406–2408), that treating a patient who weighed 80 kg with the dose used in the paper for a median of 40.4 weeks would add between $42,800 and $55,000 (34,300–44,100 euros) to the cost of their care. "Unfortunately," writes Schrag "such costly treatment will not provide a cure; one can only speculate about the relative effect of directing these resources towards screening and prevention."

Mike Keighley, chairman of the Public Affairs Committee of the United European Gastroenterology Federation (UEGF), argues that the introduction of widespread screening programmes would deliver a far greater impact on overall survival from CRC than treating end-stage disease. He quoted results from a recent 18-year Danish Screening Programme by Professor Ole Kronborg, from Odense University Hospital, suggesting screening with a faecal occult blood test (FOBT) reduced CRC deaths by 43% for individuals who had participated in the full 18-year programme.

Still no screening?

"Estimates suggest that if we could get FOBT uptake rates of 70% we could halve the death rate of CRC, while the evidence that the new drugs are hugely superior is lacking," said Keighley. "It could be argued that treating metastatic disease is shutting the door after the horse has bolted.

"But screening is up against the problem that public health experts have a low presence compared to powerful patient lobbies."

It is a question of priorities, and Keighley believes governments have got them wrong. He points out that although screening for CRC became EU policy in November 2003, not a single European country has yet introduced a comprehensive screening programme.

David Cunningham, a lead author on the cetuximab paper, from the Royal Marsden Hospital, London, agreed that ongoing efforts in the area of screening are crucial, but stressed that they should not be counterposed to attempts to improve outcomes for patients who present with advanced disease, and efforts in the two areas need to occur in parallel.

The challenge for the future, both maintain, is to define the populations who are most likely to benefit from new therapies. "This would ensure both appropriate use of resources and minimisation of adverse effects," said Cunningham. Studies with cetuximab show a correlation between the development of a maculopapular rash (a characteristic side-effect of EGFR blockade) and the likelihood of a positive response, which Cunningham believes could potentially be used to determine which patients may benefit from therapy. However, he stressed the need to await the results of prospective evaluation study that is currently in progress, and added that "emerging data and data from the studies suggest that the level of EGFR expression does not correlate with response, and EGFR expression alone may therefore not be the most appropriate method to select patients for therapy."

Van Cutsem said that his group was undertaking tumour biopsies of patients treated with cetuximab, to see whether the presence of different enzymes, such as MAP kinase and AKT, might predict outcome.

Labianca believes that in the mean time clear guidance is needed for oncologists faced with making costly decisions. "The scientific societies, such as ESMO in Europe and AIOM in Italy, need to give clinicians a steer with the establishment of guidelines for the treatment of CRC that can be updated according to each advance," he said.

On the basis of the trials, he added, there are now two settings where the new agents might be offered. He felt it reasonable that cetuximab might be offered second or third line after irinotecan escape, and that bevacizumab, combined with irinotecan-based chemotherapy, might provide first-line treatment for patients in whom it was hoped to produce curative effects.

"Clinicians need guidelines for CRC treatment that can be updated with each advance"

Flims: Building the next generation of clinical researchers

Stuart Bell

Conducting clinical trials is essential to the development of new cancer treatments, but there are many pitfalls, and it takes knowledge and experience to get it right. Where do Europe's young oncologists go to pick up the necessary skills? Until 1999, there was nowhere.

IN 1994 two leading US clinical oncologists, Daniel D von Hoff and Charles A Coltman Jr, realised that there was a serious shortage of translational / clinical investigators who could design and conduct the clinical trials necessary to assess new therapeutic agents under development.

They were concerned that not enough physician investigators were following careers in patient-oriented research. So they made proposals for a special course designed to train young clinical investigators in the fundamentals of clinical trials design.

In 1996 the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) responded to their suggestions by creating the first Methods in Clinical Cancer Research Workshop, which was held in Park City, Utah, although all subsequent workshops have been held in Vail, Colorado.

In 1997, among the faculty members of the Vail Workshop was a certain Jean-Pierre Armand, from the Institut Gustave-Roussy in Villejuif, France. He was impressed, and recognised the need for something similar in Europe. So he invited the Federation of European Cancer Societies (FECS) to take the lead in establishing a European equivalent. Together, FECS, ASCO and AACR saw a great opportunity for a parallel Methods in Clinical Cancer Research Workshop held in Europe, which, they reasoned, would allow additional highly qualified, highly motivated young clinical investigators to take the course and would increase interaction between US and European clinical researchers through direct contact at the Workshop.

So in 1999 FECS organised the first European Workshop (jointly sponsored by AACR and ASCO) in the town of Flims, Switzerland. It quickly established itself as one of Europe's leading educational oncology forums. The main aim of the Workshop is to develop a cadre of well-trained, experienced researchers whose expertise will foster better clinical trials design, thereby hastening the introduction of improved regimens for cancer therapy into everyday medical practice and patient care. The Workshop has a famously high academic standard, fostered by the involve-

The class of 2004. Hopes for expanding our knowledge of cancer and cancer therapies over the coming decades rest on people like these

The great majority of Flims graduates become increasingly involved in clinical research

ment of a world-class, multi-disciplinary faculty encompassing leaders in the fields of clinical research, translational research and biostatistics. The core faculty consists of representatives of FECS, AACR and ASCO, ensuring that students receive guidance from both European and US perspectives. The Workshop is designed with a high faculty-to-student ratio so the students have ready access to their mentors, usually with groups of seven to ten students being mentored by two clinical investigators in conjunction with a biostatistician. This gives Workshop participants a full week of ready and uninterrupted access to the leaders in the field, ensuring an almost unequalled transfer of knowledge in a workshop setting, and helps to build long-term working relationships and friendships that enhance clinical trial design and implementation for the future.

Brainstorming

The Workshop is structured to maximise the potential for students to apply the skills they learn in a practical setting following the completion of the course. For example, part of the application procedure involves submitting, in advance, a concept for a prospective clinical trial to be developed during the Workshop. This concept must be new, ethical, and feasible and also be fully supported by the applicant's mentor in their home institute. During the Workshop the concept is developed into a scientifically sound clinical trial protocol that the student will subsequently endeavour to activate in their home institute. The development of this submitted concept into a clinical trial protocol forms the core of the Workshop. The design and refinement of each student's protocol is undertaken in small groups, which form highly interactive brainstorming sessions, and is also undertaken individually during sessions designed to allow the student to concentrate on their protocol, whilst calling on the available faculty experts for guidance on specific issues. To complement the clinical trial protocol development of the Workshops, students also receive specific training on how to get their protocol accepted, activated and sponsored. This guidance is

Students propose their own clinical trials and work in small groups to develop the designs and protocols

essential, given the complex regulation and bureaucracy involved in the activation of a trial.

Flims students also attend a range of lectures on all aspects of clinical trial design, covering biostatistics and ethical principles along with more detailed topics such as pharmacokinetics, tumour measurement, drug registration and clinical trial endpoints. These lectures, given by the faculty members, serve to provide a comprehensive theoretical background in all aspects of clinical trial design. The high level of support and mentoring that characterises the Workshop continues long afterwards: faculty members remain in close contact with their students, guiding them through the process of sponsoring and activating their protocol and maintaining an interest in their careers. This dedication by the faculty reflects the spirit of collaboration and commitment to education that the Workshop embodies.

The success of the Workshop lies in the combination of a world-class faculty, its unique format and the expectation of the transformation of a clinical concept into a real research protocol. The selection of Flims students has become a rigorous process designed to select a diverse group of young oncologists who will derive the greatest benefit from the experience and then successfully apply their knowledge to clinical trial protocols at cancer research and treatment centres across the whole of Europe and throughout the world.

More than 500 students from 36 countries have participated in the Flims Workshop since it started six years ago. When added to the numbers who have participated in Vail, there are now more than 1,000 alumni from these Methods in Clinical Cancer Research workshops. This represents a considerable strength of clinical trial expertise, and the majority of these Flims alumni continue to be actively involved in patient-oriented research.

From protocol to practice

A recent survey of Flims fellows revealed that the majority felt that participation in the Workshop had not only advanced their career, but had also stimulated them to continue working in clinical cancer research. Of those who have now been monitored for five years, the great majority have become increasingly active in clinical research and in advancing the field of cancer therapy. Specifically, the survey revealed that approximately 50% of protocols developed during the Workshop were submitted within two years to the local Ethics Review Committee. Of these protocols, 94% were approved by the Committees, with 76% of them

A full week with the leaders in the field ensures an unequalled transfer of knowledge

being implemented at the student's home institution. Within a year of completing the Workshop, around 40% of the students had one protocol (and 30% had two or more protocols) submitted and implemented at their home institution. These figures reveal the extent to which the Workshop has a beneficial impact on clinical trials in Europe. So far, however, because of the relatively recent establishment of the Workshop, few of the implemented studies have come to maturity and been published or presented at conferences. This is set to change over the next few years.

Flims alumni club

Of the young oncologists who have attended the Workshop, a large number expressed the need for a forum where they could focus their continued involvement in clinical and translational research. To cater to this need, a group of past Flims participants started the Flims Alumni Club (FAC). Established in 2001, FAC has a wide range of aims, all intended to promote the active involvement of young cancer specialists in clinical and translational research. It provides a forum where young cancer specialists of all disciplines can develop collaborative networks, whilst encouraging a multidisciplinary approach and disseminating information on clinical cancer research. FAC has recently been accepted into FECS as an Affiliated Member, which means that FAC will have a representative on the FECS Council and will be entitled to have representatives on official FECS committees and other bodies including the Accreditation Council of Europe (ACOE).

Looking forward, FAC is keen to establish partnerships and synergies with other organisations that share its aim of teaching young European cancer specialists good research and clinical practice. It has begun a collaboration with the European School of Oncology (ESO) in reaching out to promising young cancer clinicians. The two organisations will each encourage their members to make use of the educational opportunities available in their partners' programmes. FAC members will participate as tutors in the 2005 ESO Masterclass, and FAC will sponsor five travel grants for Masterclass participants from poorer countries. FAC also continues to sponsor participation in the Flims Workshop.

The Flims Workshop on Methods in Clinical Cancer Research is a valued and respected educational forum that adds strength and depth to the European oncology community, and helps to ensure that the future of clinical trials in Europe is secure. It is reassuring that so many young oncologists want to attend the Workshop, and reassuring too that so many Flims students manage to successfully activate their protocols and demonstrate a commitment to stay in patient-oriented research. The success of the Workshop is a testament to the vision of the founders.

High teacher-to-student ratios lead to lasting relationships

Flims 2005 application details can be found at http://www.fecs.be (application deadline; 14 February 2005)

Just the job?

It's time to try out the new disability rights laws

Anna Wagstaff

By now, all EU Member States should have outlawed discrimination at work on the grounds of disability. Will this be enough to protect cancer patients from being forced out of their jobs, and give them the right to continue working at the level they want? If not, now is the time to contact the Commission and complain.

October marked the deadline for European Union Member States to introduce legislation outlawing discrimination at work on the grounds of disability. How this legislation will affect cancer patients remains unclear. Typically of EC Directives, the European Employment Framework Directive is short on detail, leaving key concepts, such as the definition of 'disability', for each Member State to decide. To date there are six countries that have failed to implement the Directive at all, while many of the countries that claim to have implemented it may in fact fall short of full compliance.

Over the coming year, the EU will be reviewing the measures taken by Member States, and may take action against those that are out of compliance. If the laws don't protect the rights of cancer patients to remain in paid employment, then lobbying the EC over the coming months may help ensure the necessary improvements are made.

Fighting disability discrimination at work is not usually associated with cancer patients. Traditionally, this has been taken up by people with physical disabilities and, increasingly, by people with learning disabilities. Cancer activists, by contrast, have concentrated on research, treatment and care. Yet when more than 100 delegates from across Europe gathered for the first meeting of the European Cancer Patient Coalition in Milan this June, discrimination in the workplace generated more heat than any other issue.

Delegates who had remained silent for the rest of the weekend lined up to tell their stories. Common to many was a continuing sense of bitterness.

One delegate, from Austria, talked about his attempts to move to an office job after prostate surgery left him with mild incontinence. "I was all day on the road, with a 15 kilo pack, and after the second customer, on the second floor, I was wet." All larger companies in Austria have a disabled workers' representative, so he went to ask for support from the one at his workplace. He found none. The representative, a man who had lost a hand, said, "You've got two arms, you've got two legs, you're not blind, you can hear and you're not in a wheelchair. What's the problem?"

Patients often see keeping their job as an indicator that there is a future ahead of them

Another delegate, from Ireland, was forced from his job as a commercial artist because the combined effects of treatment for prostate cancer and chronic asthma left him needing a short nap half-way through the day. "So long as I can lie down for half an hour, my batteries can recharge and I can work with no problem whatsoever," he said. He felt he had been treated unfairly, but doubted he would have got anywhere by taking a case for discrimination: "My employer would simply say: 'This guy keeps falling asleep at work.'"

Feeling worthless

Similar experiences were reported from Germany, where one delegate complained of a vicious cycle in which cancer patients suffer stress and depression associated with their disease, which can affect their work. Employers who are not supportive and understanding put further pressure on the patient, by making them feel that they are worthless and not pulling their weight. "Even if they have every right to remain in their job," she said, "the company will offer them money to leave, and usually they end up leaving."

The stories from the European Cancer Patient Coalition seem, sadly, to be representative of what happens throughout Europe. Vesela Kapitanska is a breast cancer survivor who works as a family therapist in the Cancer Patients' Association in Bulgaria, where protection for workers rights has traditionally been strong. She tells of a cancer survivor, Tzveta Manikatova, who has been forced out of her job because of heart disease she contracted while undergoing radiotherapy following a mastectomy five years ago. Before her cancer diagnosis she had been doing a physically undemanding job at the Bulgarian Telecommunications Company. After her treatment, she returned to work, and for five years everything was fine. But when the company was recently privatised, a new manager took over. He told Manikatova and other workers with chronic health problems to sign a 'voluntary' redundancy agreement or be discharged without compensation after three months. With two children to care for, and a husband who was earning less than she was, she had no choice but to take the compensation, and is now looking for alternative work.

"It's not just an economic problem," says Kapitanska. "Most cancer patients want to return to their jobs to forget about the troubles they had and get back to their friends and normality. Working keeps them busy and stops them dwelling all the time on their disease. It also makes them feel useful and able to contribute, rather than ill and dependent."

Sandra Hunton, Director of a cancer support centre in Bradford, UK, strongly agrees. "Patients often see keeping their job as an indicator that there is a future ahead of them. They try to hang on because they have to believe that they are going to get well and will go back to work. Losing your job is a bit like losing the future. It's a bit like giving up."

Hunton has learnt from experience that even if employers are trying to force you out of the door, giving up your job is often not the best move. "Sometimes family or nurses and doctors, with the best of intentions, advise people to give up work, because they are caring and don't want the patient to be worried. But it may not be the best thing to do, for economic reasons or psychologically."

Marginalised

Elisabetta Iannelli, an Italian attorney, has represented many disabled and ill people on employment and benefits issues, and is herself a cancer survivor. She has written a guide to the rights of cancer patients.

At the Milan meeting, she insisted that the right to work is essential. "Imagine a 45-year-old man, with a family. He is diagnosed with cancer

but treated successfully. Then there is another threat. If he loses his job, he may become depressed, marginalised, a burden on his family. His family may also be discriminated against. Medicine gives him back his life, but society gives him other problems."

"We want to keep on working. It should be possible to change from full-time to part time jobs and afterwards maybe to change back again."

It is clear that cancer patients across Europe face similar problems at work. But can the European Employment Directive provide an effective remedy? "Probably yes," says barrister Catherine Casserley, who is senior legal advisor to the UK Disability Rights Commission, "But only under certain conditions."

For cancer patients, a key issue is how Member States choose to define 'disability', which is not spelled out in the EC Directive (see box, pages 50-51). Ireland, for instance, has a broad definition, and its legislation would clearly cover cancer patients. In the UK, by contrast, the definition is far more restrictive, and the majority of discrimination cases that have failed since the UK Disability Discrimination Act for employment came into force in December 1996, did so because the person was deemed not to fit the criteria. One employment tribunal ruled that a man with mild incontinence following surgery for prostate cancer was not disabled. He won his appeal, but only after he was obliged to reveal in court information so personal that he had never even talked about it with his wife.

Taking cases

Even with a well-framed law, however, many people will be unaware of their rights, or lack the confidence and money to take a case. "If the law is to be effective," says Casserley, "there has to be a body like the Disability Rights Commission in the UK that is responsible for raising awareness and has the power to take cases against employers."

Most important of all, she says, is that people facing discrimination take a stand. "The only way cancer patients are going to get anything out of this legislation, is if they use it."

Casserley cites two examples. A man had been accepted for a job at a large company as a senior software coordinator. While on holiday before starting his job he was diagnosed with multiple myeloma. He told the company he needed immediate treatment and explained his start date would be delayed. The company withdrew the job offer.

The second example involved a man who developed cancer while in employment. He told his employer he would need four weeks off. The employer said, "We don't think we can use you after you come back."

"Because of the Disability Discrimination Act," says Casserley, "we were able do something about both cases. In the first case, the man got another job, and the employer paid £12,000 [17,350 euros] for injury to his feelings. In the second case they withdrew the threat of dismissal."

The European Directive covers discrimination on the grounds of religion, belief, disability, age or sexual orientation. It lays down a principle of equal treatment, which it defines as 'no direct or indirect discrimination'. This means that you cannot be treated differently from a colleague merely because of your disability (direct discrimination), unless it is strictly relevant and there is no reasonable adjustment that can be made to help the person do the job. It also means that companies may not use criteria, provisions or practices that effectively discriminate against people with disabilities, unless they are able to show that the aim is legitimate and that it cannot be achieved by any other means (indirect discrimination).

The only way cancer patients are going to get anything out of this legislation is if they use it

The most important provision obliges employers to make changes to the way they organise the work

For cancer patients, the most important provision is probably the one that obliges employers to make 'reasonable accommodation', in other words, to make changes to the way they organise the work to make working easier for employees covered by the Directive. This explicitly includes adjustments to 'patterns of working time and the distribution of tasks' if necessary. The right to switch, temporarily or permanently, to part-time working is not spelled out, but there is a strong basis for arguing that such a right is at least strongly implied in the wording of the Directive.

Casserley is convinced that, despite the vague terminology, the 'reasonable accommodation' requirement will provide protection for cancer patients and others. But she says that many European judges are sceptical. "They find it hard to get to grips with the idea that you can require an employer to change the way they work. But that is what they have to do."

Pyrrhic victories

As with other employment legislation, there will be a gap between what the law says and what

SPAIN

Ley de no-discriminación y accesibilidad universal para personas con discapacidad 2003 (Article 1 para 2)

(Anti-discrimination and universal accessibility for disabled people Act 2003)

"For the purposes of this law, disabled persons shall include all those who have a grade of handicap of 33 per cent or above. In all cases, any person receiving a social security pension for a permanent incapacity graded as a total, absolute or serious handicap, as well as any person receiving a social security pension having been retired from work due to permanent incapacity shall be considered as having a grade of handicap of 33 per cent or above."

This is one of the more restrictive definitions, which would exclude most cancer patients from being covered by the law.

IRELAND

Employment Equality Act 1998

Disability is defined as "the total or partial absence of a person's bodily functions, including the absence of a part of a person's body, (b) the presence in the body of organisms causing or likely to cause chronic disease or illness (c) the malfunction/malformation disfigurement of a part of a person's body (d) a condition or malfunction which results in a person learning differently from a person without a condition or malfunction or (e) a condition, illness or disease which affects a person's thought processes, perceptions of reality, emotions or judgment or which results in disturbed behaviour, and shall be taken to include a disability which exists at present, or which previously existed but no longer exists, or which may exist in the future or which is imputed to a person."

This is a broad definition. Although very medically based, it does not require the person to have a condition for a particular length of time, nor does it require a certain degree of symptoms. This means there are few disputes, if any, about whether or not someone meets the definition.

employers do. One of the UK delegates to the Milan conference argued that many 'successful' actions under the anti-discrimination legislation were pyrrhic victories. "The cases were won, and compensation was paid, but the employees still lost their jobs."

Worse still, many cases never even make it to a tribunal. Alison Rooks, who works as a benefits advisor at Bradford Cancer Support, says that workers are often nervous about taking up the issue and asking their employer to change the way they work. "The question is whether people have the energy and confidence to challenge their manager, and take a case through a tribunal, at the very time when they have to devote their energies to struggling with the disease."

The situation is not helped by low levels of unionisation, and poor provision of good-quality free advice on employment matters.

UNITED KINGDOM

Disability Discrimination Act 1995 (section I)

"A person has a disability for the purposes of the DDA if s/he has a physical or mental impairment which has a substantial and long-term adverse effect on his or her ability to carry out normal day to day activities."

'Long term' *is defined as* "lasting 12 months, likely to last for 12 months or for the rest of the person's life" *(if their lifespan is likely to be less than 12 months)*

'Normal day to day activities' *is defined as* "mobility, manual dexterity, physical co-ordination, continence, ability to lift, carry or move everyday objects; speech; hearing; sight; memory; the ability to learn, understand or concentrate; the perception of risk or physical danger"

The definition also covers those with 'progressive' conditions, if they have some symptoms and the condition is likely to develop so that it will in future meet the full test of definition of disability.

This definition has the scope to be broad, depending on how the courts interpret it. The time limit may be a problem, for instance, for patients experiencing cyclical episodes of acute illness and remission

Rooks cites a recent tribunal in which a woman won financial compensation after being edged out of her job following cancer treatment. Ironically, the employer was a medical General Practitioner.

So how much is the European Directive really worth? A great deal, according to Casserley. "The real successes are the cases we don't hear about, because they don't come to court. People ring up, they find out about their rights, and they say to their employers: 'You can't do this to me.' It's at that point that it has the most effect. That's why it's important to raise awareness so you solve these situations before they get that far."

The point was well taken in Milan. Yet, it was also clear that joining a broader campaign for fair treatment at work involves defining where cancer patients fit into the disability lobby. Many people with disabilities and chronic conditions like epilepsy see their disability as an important element in how they define themselves. Most cancer patients, in contrast, refuse to allow the cancer to define who they are. For many patients, defining themselves as 'normal' and 'healthy' is an important part of defeating the disease and of putting the trauma of diagnosis and the misery of acute treatment behind them.

Yet cancer patients do often suffer effects from illness or treatment, including fatigue (which affects up to 80% of patients), lymphoedema and other circulatory problems, and incontinence. If these are to be recognised under discrimination legislation, they have to have some kind of a name. "I prefer the term 'impairment' to disability," said one delegate. "I'm not sure we want to be called handicapped or disabled or impaired," said another. In the end, it was agreed that the discussion of how cancer patients should define themselves should be revisited at a later date. (Such a discussion has long been going on in the wider disability movement, which would argue that while people may have impairments, they are only handicapped by other people's ignorance or prejudice.)

HOSTILE RECEPTION

Delegates from Austria and Italy reported a hostile reception from some national disability

People with disabilities or chronic illness must be the ones who take decisions about themselves

organisations. "The trouble is," said the Austrian delegate, "organisations and laws for disabled people in Austria centre on the needs of veterans from World War II – they are brilliantly organised, it works for them, and they don't want to let us share it."

However, this attitude does not seem typical, and indeed there are many other people with disabilities that do not involve the loss of a limb or an obvious physical impairment who have lobbied effectively at a European level.

Carlotta Besozzi, Director of the European Disability Forum (EDF), services a committee that was recently established to deal exclusively with the needs of people with chronic illnesses.

Besozzi says that the situation varies across Europe. In Sweden, for instance, people with chronic illnesses – including people who suffer allergies – have long been considered as people with disabilities. She also cites the Netherlands as an example of a country which has set up a single national platform explicitly for "people with disabilities and people with chronic illness".

Besozzi says, "People on our committee would also say that many people with chronic illness do not want to consider themselves as disabled and many of the organisations have in the past focused a lot on research issues and health issues. It is quite a new move that there is a growing interest in employment and rights in society, social inclusion. It's an ongoing discussion."

Does she feel the European Directive has something to offer cancer patients? "I think the legislation will have an impact. Not only should it protect you against discrimination because of your health situation, but it requires that your workplace be adjusted to help you work to your full potential. These are important issues for cancer patients."

She says that the EDF would be willing to cooperate and work with cancer patients' organisations. "The important issue is that people themselves, whether they are with disabilities or with chronic illness, are the ones who take decisions about themselves. We want to make sure nothing about us is decided by somebody else."

Cancer patients are beginning to find their own voice. They should now use it to ensure that in every country the Directive is implemented in such a way that it protects their rights at work.

This will mean working with other patient and disability groups to raise awareness of the legislation, to take test cases, and to submit complaints to the European Commission, if the outcomes of these cases indicate that the legislation falls short of the terms of the Directive. Helping people make full use of the legislation will also be important. This means not just patients, but health workers, trade unions – and employers – need to be aware of the legislation and give support to patients who need it.

The ultimate aim in all countries must be an employment culture that is far more inclusive and supportive of the needs of workers with cancer and other chronic illnesses.

For information and advice about the the Directive, about national disability discrimination laws and national disability organisations, and about how to complain to the European Commission, contact the European Disability Forum at **info@edf-feph.org** *or by telephone on* **+32 2 282 4600**

Ireland's bumpy road to a world-class cancer service

Peter McIntyre

Having scored a first by extending smoking bans to pubs, cafes and restaurants, Ireland is now grasping the nettle of centralising specialist cancer services. The strategy has met some resistance, but it's hard to argue against a measure that promises up to a 20% drop in mortality.

At the turn of the year the Republic of Ireland will publish its second National Cancer Strategy in a decade. The first Strategy saw a huge increase in funding and staffing for cancer services, and succeeded three years early in its aim of cutting the death rate. The second Strategy promises a revolution in the way that cancer care is delivered to the four million people of the Republic.

With one meeting left of the National Cancer Forum, the shape of the second National Cancer Strategy is pretty well decided. Cancer services will be configured in a pyramid of care, most likely based on four regional networks, two centred on Dublin in the east of the country, one on Cork in the south and one on Galway in the west.

It is a plan to create centres of excellence where the 20,000 new patients diagnosed with cancer each year will receive multidisciplinary care, and be treated by consultants with real expertise in their particular cancer. This time it is unlikely there will be a huge increase in resources, but the Strategy aims to generate a second giant step forward for services that ten years ago were patchy, parochial and non-specialised. This approach has the support of the Government, most professionals and the main cancer charities and patient groups. But it is resented outside the chosen centres, where some patients will have to travel long distances for treatment.

This Strategy has already had a dress rehearsal. In October 2003, an expert group published a report on the development of radiotherapy services in Ireland. This also recommended a national network based on four supra regional centres. It called for a massive increase in the number of linear accelerators, from 10 to 26 by 2008 and to 35 or more by 2013. The Government accepted the report.

This increases the number of radiation oncology centres from two (University Hospital, Cork, and St Luke's Hospital, Dublin) to four (another one in Dublin and a new unit now being built in Galway). However, people in Sligo and Donegal in the north west of Ireland will have to travel to Galway or across the border to Belfast for radiotherapy, while in the

DYLAN VAUGHAN

Demonstrators calling for a radiotherapy unit in Waterford "bombarded" Bertie Ahern, Ireland's Prime Minister, with daffodils

south east a population of 450,000 people will have to look north to Dublin or south to Cork.

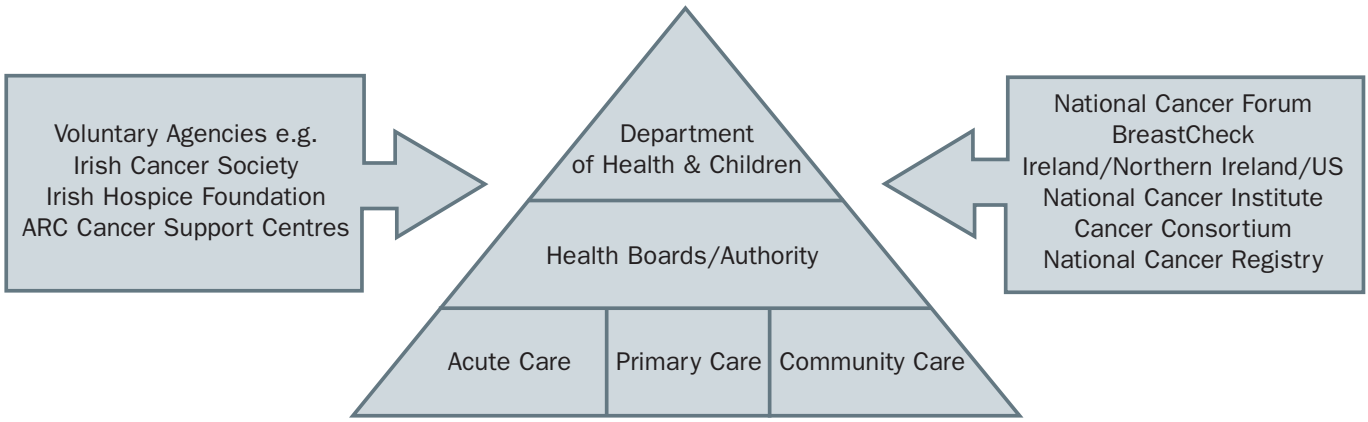
Large demonstrations were held in the south-east this year to demand that Waterford Regional Hospital be given its own radiotherapy unit. One demonstrator was Mary Power, who had undergone surgery for bowel cancer at Waterford in April 2001 followed by radiotherapy in Dublin. She told the *Munster Express* how she would leave home at 6.30 am to catch a 7.20 am Waterford train to Dublin, then take two buses and walk to St Luke's where her radiotherapy treatment would last less than five minutes. She would immediately set off again for home. She did this journey five days a week for five weeks. Mary said: "You'd be feeling so rotten from the day before but you knew you had to tear yourself out of the bed and start again the next morning. So many times I was violently ill on that train. I'd arrive home exhausted and then have to start all over again." When she contemplates the possible return of her cancer, it is the journey to Dublin she chiefly dreads.

A local service was a significant issue in local elections in Waterford. Faced with a choice between excellence and local services, many people ask, "Why can't we have both?"

Paul Redmond, Professor of Surgery at Cork University Hospital and chair of the

When she contemplates the possible return of her cancer, it is the journey to Dublin she chiefly dreads

STRUCTURE FOR THE DELIVERY OF IRELAND'S CANCER SERVICES



Source: An Evaluation of "Cancer Services in Ireland: A National Strategy 1996", Deloitte, 2003

National Cancer Forum, believes that this patient philosophy is starting to change. "There is an attitude in Ireland that we have a right to a Memorial Sloan-Kettering in our back garden so to speak. We have a local hospital and it should be able to do everything.

"People are now more familiar with the whole concept of case volume, evidence-based practice and the centralisation of services for certain aspects of cancer care. People are more accepting of the idea that for certain parts of my care I am going to have to travel, and the likelihood is that it has been done to improve my outcome."

Controversy should not obscure the progress that Ireland has already made. When the first Cancer Strategy was launched in 1996 there were only four medical oncologists in Ireland. Now there are 19. The Strategy has delivered 87 new cancer consultants, including 14 breast surgeons, 6 general surgeons, 19 histopathologists, 12 radiologists and 8 palliative care specialists.

Prior to 1997, nurses working in oncology were not fully recognised. By 2003 there were 245 clinical nurse specialists, 170 appointed in 2001 alone. Half of these nurses are working in palliative home care.

Each new consultant represents a cancer team costing 1–1.5 million euros a year. In 1997 spending on cancer services was 7.45 million euros a year. By 2003 this had risen by 1,477% to 117.45 million euros – a cumulative increase of approximately 400 million euros over the lifetime of the Strategy.

The BreastCheck screening programme was introduced for women aged 50–64 and is being expanded to the whole of the Republic. The first Strategy can also take credit for a 42% increase in patient treatment between 1995 and 2001.

The key goal was to reduce the death rate from cancer in the under-65 age group by 15% in the ten-year period from 1994. In the first few years, Ireland was steadily on target to achieve this. Then 2001 saw a dramatic fall of more than 5% in one year, and the target was achieved three years early.

One factor behind this success was the decline in smoking, and, encouraged by these results, Ireland did what no other country dared. In March 2004 it barred smoking from all workplaces, including pubs, bars, restaurants and cafes. Cigarette manufacturers, Gallagher, reported a fall in sales of 7.5% in the first six months of the ban, suggesting a full year dividend of 500 million fewer cigarettes being smoked by the population of Ireland. Meanwhile, in the UK, Ireland's timid neighbour, sales rose by more than 3%.

An evaluation of the first Cancer Strategy by Deloitte and Touche management consultants, published in 2003, was generally favourable, but concluded that further improvements were needed, without comparable spending increases. Deloitte says the new Strategy will have to rely on "an ability to reconfigure present structures, enhance system co-ordination and interaction and redefine accepted working practices and service management."

This was underlined by a National Cancer Registry report in 2004, which found significant regional variations in treatment and, in the case of breast and colorectal cancer, significant differences in regional survival rates.

Redmond contrasts the second Strategy with the "cluster bombing" of consultants, nurses and new services that came with the first. "This second Strategy will look at putting together a cohesive plan for how cancer care is actually delivered in a more uniform way throughout the country, so that you do not have heterogeneity of care and, ultimately, heterogeneity in terms of outcome. It is not going to cost anything like the first Strategy."

"The goal will be organisational infrastructure, governance in terms of how we deliver cancer care, audit, and very careful assessment. If you are a dedicated breast centre you will have to be able to show that you are improving outcomes for patients. Of course there will always be investment for cancer care and there has been a promise of that. But I don't think that this Strategy's purpose is to say we want another 250 million euros or whatever."

The National Cancer Forum will propose four networks of cancer services, each covering a population of about one million people. At the heart of each network will be a lead cancer institution or specialist cancer hospital, where radiotherapy services will probably be based. These centres will deliver a full range of cancer care, and will oversee the delivery of cancer services at the other institutions in the network.

Each network will also have regional centres or cancer units, dealing with cancers where a high degree of specialisation is not so important.

A third tier will offer primary care, palliative care, support and less complex chemotherapy.

Redmond is a Dubliner who spent two years doing surgical oncology in Philadelphia before returning to Ireland. He moved to Cork in 1997 as the first Strategy was under way. The three hospitals in Cork have already created departments that cut across the bureaucratic boundaries. Cancer teams meet across the city, audit their cases together and have even drawn up their own clinical guidelines.

Redmond says that most cancer care should be in the hands of multidisciplinary teams specialising in particular cancers.

"For certain types of cancer, breast cancer for example or rectal cancer, it appears that your surgeon needs to be doing a high volume of cases for you to have your best chance of doing well. If you are a breast surgeon you should operate on a minimum of 50 cancers a year. For other cancers it is more about the patient being processed through the system in a multidisciplinary way so that care is delivered objectively, and the case is discussed by all members of the cancer care team.

"It is like flying in a plane. You don't get in with a pilot who says 'I have not flown this for a year but we'll give it a go'. If someone says 'I have not done a breast cancer operation for a year but I read it up last night in the book and I am confident I will be able to do it again,' you are going to run out of the clinic.

"Historically, when you were appointed as a general surgeon you were trained to do bowel surgery, breast surgery, stomach surgery, oesophageal surgery, whatever. Your remit was

"You don't get in with a pilot who says 'I have not flown this for a year but we'll give it a go.' "

Centres of excellence could cut cancer mortality in Ireland by 20%

to deal with everything that walked through the door. Redefining work practices means not trying to do everything for everybody, probably not as well as you should.

"Individual clinicians need to identify their strengths. You become a disease specific clinician rather than O'Brian or Murphy doing four or five cases of this a year and four or five cases of that. Instead, you work in the breast team or the colorectal team and you go to the multidisciplinary meetings and interrelate with the nurse specialist."

The health structure of Ireland is changing and the tide is in favour of the new Strategy. Ten health boards disappear at the end of the year, probably to be replaced by four health regions, two centred on Dublin, one on the south of Ireland and one on the west. A new Health Service Executive will exert pressure to raise standards throughout the country.

The Strategy will have the backing of the Irish Cancer Society, which says that centres of excellence could cut mortality by 20%. The Society acknowledges concerns of patients in Limerick and Waterford in the south and Sligo and Donegal in the north west, but concludes: "Although services should be delivered as close to the patient's home as feasible, the over-riding priority should be to provide the best, safest and most effective treatment and in doing so to provide the best opportunity for long-term survival."

Redmond believes that most people will welcome the changes. "The evidence for the multidisciplinary approach and the case volume approach is so strong now that nobody can really say it is wrong. It doesn't take a rocket scientist to work out that if you go to a clinic doing a lot of the disease with all the infrastructure and staff and equipment, you are more likely to be alive in five years. So when I go to the National Cancer Forum and sit down with 24 people there are few dissenters and most agree that we need to do it. Everybody argues a bit about the infrastructure but we have almost got those problems ironed out as well."

However, he worries that patients in Ireland may expect too much. "There is no doubt that the delivery of cancer care has hugely improved in this country but so also has patient expectation. We have perhaps an expectation that you will walk through the system and you will be cured, and you can expect nothing to go wrong, and it will be done quickly and be rosy in the garden almost to the point where it is a bit unreal.

"We spend significant amounts of time, much more than in the past, with cancer patients, which is good. My question is where will we draw the line? Where will public expectations be in five or ten years? You are never going to get it perfect."

Ireland is a place where people take decisions with the head and with the heart. The aspirations that Redmond and his team have for cancer services could put Ireland up there with the best of European oncology. Somehow, the Strategy must also deliver an acceptable solution for Mary Power and patients like her.

Where will we draw the line? You are never going to get it perfect

Access all areas

Scientific publishing is having to change rapidly to respond to growing pressure for free access to published research.

IN a letter penned in 1676, Isaac Newton famously wrote, "If I have seen further it is by standing on the shoulders of Giants." Although it is debatable whether Newton was being modest or making a barbed comment towards his correspondent (a competitor of short stature) the phrase epitomises views of how science progresses – with the speedy and open publishing of discoveries so that others may make use of them to push back the frontiers of human understanding.

For centuries, printed journals destined for university libraries have been the focus of this publishing activity. The winds of change, though, are sweeping through these quiet and dusty corridors. Because of the Internet, cost and distance are no longer barriers to providing the results of research to more than just a restricted and privileged few. This is leading people to ask why those results are not, in fact, freely available to all.

An impressive industry has built itself around the dissemination of academic research – particularly scientific work. There are over 2,000 publishers in what is called STM (scientific, technological and medical) publishing alone. Together, they publish 1.2m articles a year in about 16,000 periodical journals. It is a huge success. Not everyone, though, is entirely satisfied. Academics, universities and governments are worried that publishers have grown a little too fat and happy.

Serial killers

The problem is one of monopoly. Of course, publishing itself is an industry with few barriers to entry. That is not the issue. But certain journals are able to capture a lion's share of the important papers because researchers want their papers published in the most prestigious ones. Some titles have acquired exceptional cachet over the years. Such is their prestige that a researcher can win tenure, promotion or a research grant on the basis of a single article in the right publication.

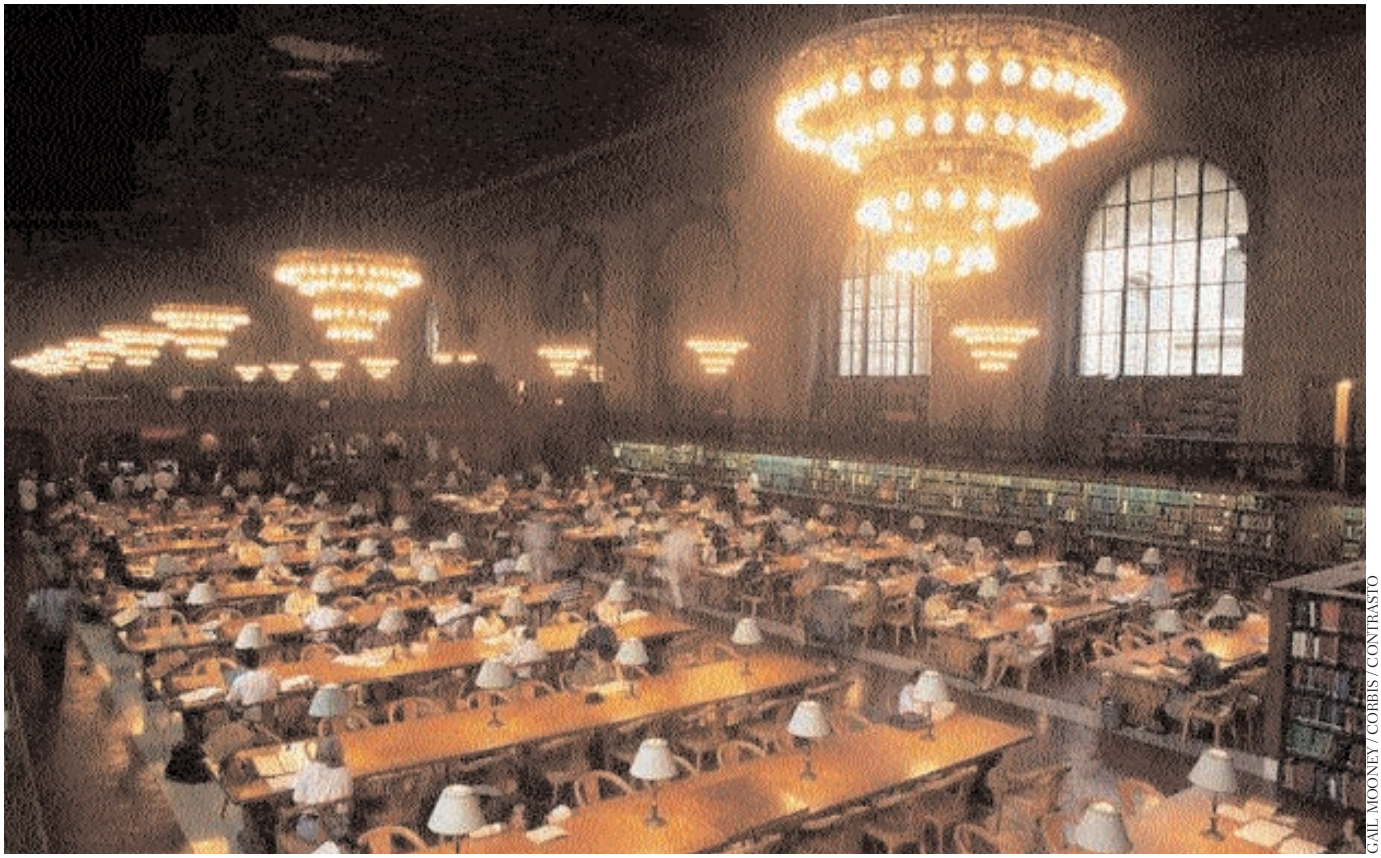
That means the publishers of those journals have the pick of the best papers, reinforcing their reputations in a positive feedback loop. They also claim copyright over what they publish, reinforcing their monopoly. So if you want to read an important paper (or an unimportant one for that matter) you have no legal choice but to pay the publisher for it.

The upshot is that university libraries must purchase the leading titles, almost whatever their price, and often at the expense of carrying less-exalted works. Owning a prestigious journal has thus become a lucrative business, which many people believe is being abused.

Cornell University, for example, recently reviewed its policies on journal acquisition. In the course of that review it noted that between 1986 and 2001 the library budget at its main campus in Ithaca, New York, increased by 149%. The number of periodicals purchased, however, grew by only 5%.

Governments, whose funds ultimately pay for a lot of the journals on the shelves of university libraries, are noticing too. A report published in July by Britain's House of Commons Science and Technology Committee found that the average price of an academic journal in Britain rose by 58% between 1998 and 2003, while the retail price index rose by 11% in that period, and scientific output

Because of the Internet, cost and distance are no longer barriers to providing the results of research



GAIL MOONEY / CORBIS / CONTRASTO

rose by 20%. The report added that profits in the industry were exceptional, singling out Reed Elsevier, a British publisher whose Dutch subsidiary, Elsevier, is the market leader in STM publishing, for having profits "as much as 34% at the operating level".

Indeed, Elsevier has attracted criticism from a number of quarters. Cornell's reviewers, for example, observed that in the previous decade Elsevier's annual price increases on its titles had often been over 10% – and occasionally over 20%.

Arie Jongejan, CEO of Elsevier's science and technology division, defends his firm's profits, pointing out that after tax and depreciation, last year's profit margins were 17%, not as high as some claim. But that is still a hefty whack. He justifies such margins on the grounds that the firm's journals are publishing more papers each year and also because high profitability is necessary in order to ensure the sustainability of those journals.

Free for all?

But the dominance of Elsevier and its kin is under attack. The House of Commons Science and Technology Committee did more than just lament the rising price of journals. It told the British government that the country's universities should be required to ensure that all their research papers are available free online, and that government-funded research grants ought to include free access to the findings as a condition of the awards. The government will respond next month*.

American politicians, too, are getting cross. Earlier this month the House of Representatives' Committee on Appropriations approved a provision in a bill that backs open access to material published by the National Institutes of Health (NIH). The committee expressed concern at the lack of public access to research findings, and at the rising price of journals. These, it commented, were "contrary to the best interests of the US taxpayers who paid for this research".

** The Government's response will be available on the Science and Technology Committee page at www.parliament.uk. It was still awaited at the time this issue of Cancer World went to press*

Owning a prestigious journal has thus become a lucrative business, which many people believe is being abused.

If the Senate approves the recommendation, it will become law and the NIH will be required to deposit research funded by the agency into an online government archive called PubMed Central within six months of publication in any journal. If this happens, it will be significant, since NIH-funded work amounts to 50,000 papers a year.

Even mainland Europe is getting in on the act. In October 2003, the leading research associations of Germany, France and Switzerland signed what has become known as the 'Berlin Declaration' – another call for free access to research findings. One of the groups behind the declaration, Germany's Max Planck Society, is now changing its employment contracts to require staff to return the copyright of their work to the society. At the moment it gets assigned to the publishers. Although the society's researchers will still be able to publish in journals, their work must eventually be put into an online repository.

In response to the Berlin Declaration, the European Commission has begun a study of the scientific-publishing market – looking at price, access to published papers, and copyright. Because 41% of scientific papers originate in Europe (compared with 31% in America), the results of this study could have a big effect on the publishing industry.

One way of addressing the concerns of politicians and university libraries is the promotion of journals in which the author pays to be published. Many new online journals are attempting to do this, using electronic publication to cut their costs. The results are then made available free to readers.

BioMed Central, based in Britain, is one such publisher. The company, which was established in 1999, has not yet broken even. But Deborah Cockerill, the firm's assistant publisher, says it is likely to do so soon, as it is growing fast. The number of articles it publishes has doubled every year. In America, a not-for-profit organisation called the Public Library of Science is employing a similar business model.

Another possibility is to generalise the House of Representatives' proposal for American medical research and allow the traditional journals a limited period of monopoly – say six months – after which they have to make all taxpayer-funded content available free online.

Understandably, the traditional publishers are not too happy about these ideas, although some of them are moving pre-emptively towards the free-after-six-months model of the future. Barbara Meredith, vice-president of professional and scholarly publishing at the Association of American Publishers, a trade group, has said that a demand for open access to research findings could undermine the sustainability of the publishing industry, and has promised to lobby vigorously against this happening.

At the moment, the entire open access literature is tiny – less than 1% of what is published according to the Public Library of Science. But if governments were to insist that the results of research they fund must be published in an open-access way, that would change completely. The days of huge profits would then be numbered. Prestige has its uses – and the open-access journals will, no doubt, establish a pecking-order among themselves fairly quickly. But for prestige at any price, time is probably up.

Understandably, the traditional publishers are not too happy about these ideas

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