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José Baselga

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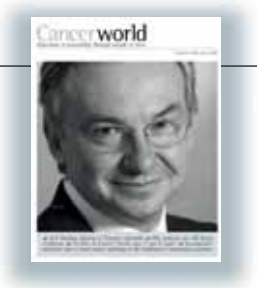

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Balancing safety against need

Kathy Redmond ■ EDITOR

When Pfizer followed Merck & co in withdrawing one of their COX-2 inhibitors from the market owing to increased risks of cardiovascular complications, it provided a timely reminder that medicines are not without their risks. We have known about the potential harm associated with medicines for centuries. Almost 500 years ago Paracelsus wrote: *Dosis facit venenum* (the dose makes the poison) – in other words, the higher the dose of any particular chemical, the greater its toxic effect on living organisms. Beneficial medicines can turn poisonous if you take too much – low-dose aspirin can reduce heart disease but higher doses can kill.

Ideally, we should protect patients from harm, but in reality, when most novel medicines are approved it is impossible to know enough about their long-term effects to enable us to do so. Gathering sufficient information prior to approval could delay access to potentially useful therapies for patients with no other options – a delay some cancer patients cannot afford. The introduction of innovative medicines requires that regulators strike the right balance between risk and benefit. With life-threatening diseases it is more acceptable to take risks with safety because so much more is at stake. Communication between pharmaceutical companies, regulators, patients and other stakeholders is essential in order to get the balance right. This is because risks are experienced and interpreted very differently depending on the perspective of the observer, and the way risks are perceived can also vary significantly depending on the situation. Once a medicine reaches the market its safety should be continuously monitored and efforts made to ensure that it is used appropriately in clinical practice. Additional clinical trials need to be carried out to clarify the effect of exposure to the medicine in 'real life' situations and to define new indications. Better mechanisms are needed for reporting adverse drug reactions and we need to raise professional and public awareness about potential safety concerns. In its recent 'Road Map to 2010' the European Medicines Agency has made a commitment to ensure that patients suffering from life-threatening conditions will gain timely access to safe and effective medicines. The Agency also aims to introduce more proactive approaches to pharmacovigilance across the EU. These developments are welcome, for it would be a tragedy if ill-informed risk-benefit analyses hindered the approval of innovative cancer drugs that could benefit thousands of European patients, or if effective medicines have to be withdrawn because we did not get the monitoring right.

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José Baselga: playing to Europe's strengths

Marc Beishon

It took José Baselga just a few years to build the oncology department at Barcelona's Vall d'Hebron hospital from a few shabby consulting rooms to a leading centre for research into targeted therapies. Europe has the edge in this type of research because we are better at working together, says Baselga. But we still have a lot to learn from the US.

The European oncology community had better get its act together – or suffer more years of fragmentation, underfunding and overburdensome regulation. It's a strong message delivered by the quietly spoken José Baselga, head of oncology at the Vall d'Hebron hospital in Barcelona, and professor of medicine at the associated medical school at the Universidad Autonoma de Barcelona.

He speaks from a position of considerable strength and experience. Not only did he spend more formative years than most immersed in one of the top facilities in the US, but he has also put Vall d'Hebron on the map as one of the major translational research and cancer treatment centres in Europe – from a standing start.

"We must realise that medical oncology is still a new field – it is not even recognised as a speciality in countries such as the UK," he says. "It is no good pretending we are strong when we actually lack strength at the European level compared to the US. But a lot of top oncology work is European in origin. I don't want to copy what happens in the US but play to our strengths, in particular our capacity for cooperation and partnership. But we need to become far more professional in our organisation, training and fundraising."

All of those factors have been promoted by Baselga in the nine years he has been in Barcelona. Half his time is taken up with the ongoing transformation of what was a tiny oncology effort into a major cancer treatment base for the province of Catalonia, such that 40% of all breast cancer patients in the region, for example, are now seen at the hospital.

The other half of his work is translational clinical and pre-clinical science – probably the area of cancer research that is weakest in general wherever you go. "We have a huge effort here on early clinical development of targeted therapeutics," he says. "We do a lot of pre-clinical and phase I trials on new compounds and we have been blessed to have been involved with a large number that are now on the market."

It all suggests that Baselga is well plugged in to both the many organisational issues that go

ELIGIO PAOLI / CONTRASTO

"I don't want to copy what happens in the US but play to our strengths – our capacity for cooperation"

With his mentor John Mendelsohn (*left*), at the MD Anderson Cancer Center, Houston, Texas, last June, where Baselga was awarded the 2004 Waun-Ki Hong Visiting Professorship

into running a cancer centre, and the clinical research areas most likely to yield promising results. There's always a certain degree of good fortune involved, but what is clear is that he has been able to marry the scientific work he built up from his time in the US with the advantages of working in a public health system in Spain.

Baselga went to medical school at Vall d'Hebron – his background at the university hospital was one factor in his eventual return. "I absolutely fell in love with internal medicine and began to be attracted to oncology." Like many, he saw cancer as a huge challenge. "But the early 1980s were fascinating times – oncogenes were just being discovered and for the first time we had the promise that the molecular basis of cancer was going to be found."

His curiosity led to a request for an 'elective' to a cancer centre, which was granted and Baselga duly asked what would be a good place to go to. "They said 'America,' and I went off to the Memorial Sloan-Kettering Cancer Center in New York, which I'd never heard of."

Initially he was accepted only for a three-month rotation, which confirmed his feeling that oncology was a fascinating subject and one he wanted to pursue. To do so in the US, however, he had to work his way back through internal medicine via internship and residency positions elsewhere in New York, his Spanish qualification not being accepted. He then applied for a three year medical oncology and haematology fellowship at Sloan-Kettering and was successful.

"In the second year of the fellowship I had to choose a mentor and was very lucky to have John Mendelsohn, then chair of medicine – he had produced the first anti-epidermal growth factor receptor (EGFR) antibodies. I became involved in laboratory studies on EGFR antibodies, and gained grants and ran clinical trials."

What happened next was the kind of break

that Baselga would now consider essential for any aspiring medical oncologist. He was offered a faculty position at Sloan-Kettering, but because of visa restrictions he was unable to take up the post until a waiver was arranged. This took about two years. "In the meantime I had no licence to treat patients and that was wonderful because I spent all my time in the lab. What happens with medical oncologists is we get pushed all too soon into clinical duties – which is what we like and what we do best – but it's important to work in the lab too." Today at Vall d'Hebron, he won't give clinical jobs to people unless they have spent at least two years in the laboratory.

"I did feel frustrated that I couldn't see patients like all my peers – but looking back it was great because I was so productive in the lab. At the time the HER2 antibodies had come out and John Mendelsohn had received Herceptin [trastuzumab] from Genentech to study. It was fascinating to see its effect on breast cancer cells and we became involved in the phase I and II trials of Herceptin, and I was principal investigator on the phase II single agent trial where we saw the first sign of activity."

After his visa waiver came through Baselga took up his faculty post, continuing his joint lab and breast service work. "I'd done the hard part and got my qualifications, green card and faculty job and I thought I'd now stay in the US. I was publishing well and the research was exciting."

But by then he'd met and married his wife Silvia, a Spanish economist and also from Barcelona. They'd had their first child and she wanted to return home, and fortuitously Baselga was sounded out for the opportunity to head the development of the new oncology centre at Vall d'Hebron. At first, it seemed like a hard decision for him. "I was involved in leading the clinical development of EGFR and HER2 antibodies and was giving up a lot. But there were frustrations in New York about the capacity to do good translational clinical science. It was extremely difficult to enrol patients in clinical trials because of the regulatory atmosphere, and tremendous difficulty in getting funding."

There were also, adds Baselga, difficulties in simply getting people to work together at Sloan-Kettering. "It was very hard for me to have, for example, a good working relationship with the pathology department. I did try very hard to run biopsy driven studies to look for biomarkers of activity in tumours – but I couldn't do it."

He puts this down to the professional and cultural structures in the US – "Still the same today I hear" – and says that team working is much better at Barcelona and indeed in other parts of Europe. "So I came here not only to build the oncology effort but also because I was convinced I could do superb translational science here – and that's been true. If you look at my CV you'll see that my best translational work has been done at Vall d'Hebron. I don't feel deprived of new compounds here – quite the reverse. Just look at the number of trials we are doing here."

> He won't give clinical jobs to people unless they have spent at least two years in the laboratory

In fact, no fewer than 55 trials were running in early 2005, including 15 phase I trials. This level of activity has not been possible in the US, which has been the subject of much soul searching. While European trials involvement is also patchy, Baselga's experience indicates that the barriers here are more easily overcome.

Baselga does, however, recognise the enormous advantages the US has in basic science and cancer care, albeit marked by a big social divide driven by the medical insurance system. "Memorial is full of excellence – they have many superb research scientists working there. They

At home with his family

have huge funding and vision and also many physicians working in clinical care. Overall, the US model has heavily influenced my career and that of many others in Europe."

The authorities at Vall d'Hebron were fortunate to find Baselga before he became too entrenched in the American research community, although he was young for such a move – just 37. "There's a point of no return once you are on the career path to full professor and your family is settled over there," he says. "Apart from the timing, I also had the advantages that I knew the hospital well, having been a student here, and am from Barcelona. But many times people come back to Spain from the US and other parts of Europe and have failed. If I'd have come back with a US mentality I would have failed too."

Certainly, he knew that the oncology department at Vall d'Hebron was the Cinderella of the hospital – relegated to a few shabby consulting rooms in an old part of the large complex, which is located on the edge of Barcelona. "First I set out to recruit my closest collaborators – people who shared my vision and were prepared to roll up their sleeves, such as the head of research at the oncology department, Joaquin Arribas, who was also at Sloan-Kettering. He was brave enough to come here to build the first oncology lab."

Next, Baselga created a clinical trials programme. "We set out to get involved in some important phase III trials, such as for Herceptin, for which I'm very grateful to Genentech. I met with the faculty and said I'd started the phase III Herceptin trial at Sloan-Kettering and we had an opportunity to translate the protocol here – an opportunity that will very seldom come along. It took many months and we were far behind – but we entered more patients in the trial than Memorial did.

"From the start we built a clinical trials effort in pursuit of excellence and it sent a signal to the oncology community, although we were lucky that the first results were positive and so we got extra visibility – we were co-authors on the *New England Journal of Medicine* papers on Herceptin.

"The other thing I did was try to instil a sense of pride in the staff who had been there for years. We had some great professionals who had little self-esteem – they were just pushing chemotherapy. I said to them: 'This is medical oncology, this is the future and you're good and we have to do a good job' – and they began to join societies and I helped them design trials of their own and get published."

At the same time Baselga was working on obtaining more resources and funding – and the rapid ramp-up of trials work was a key factor. "In 1996, we were number 23 of all the research groups at Vall d'Hebron in terms of impact [i.e. papers and citations]; by 2002 we were number one and were given more resources. It's been a huge victory – and now we are also the largest oncology trials site in Spain by far."

Between 15% and 20% of patients are now in trials – "It's easier to do research in a public health system, and Spaniards are interested in participating. We also make sure that patients in trials are very well taken care of – they get the best nurses and superb physicians." With approval and budget restrictions, enrolling in trials is also the only way that some patients can access treatments such as taxanes, he adds.

Essentially, Baselga has continued his work on molecular targeted therapies and signal pathways at Vall d'Hebron. "When I started here the only agents available were anti-EGFRs and Herceptin, but then came the tyrosine kinase inhibitors and we jumped on them, doing a lot of studies on selecting the best dose and patient

populations." His recent and current work now read like a roll call of new agents – trastuzumab, cetuximab, gefitinib, erlotinib, EMD 72000, *Ras* inhibitors and a variety of anti-angiogenic agents – and his team has pioneered combined molecular blockades, for example anti-EGFR and small molecules.

"We now only get involved in phase I trials where we are part of the science – I'm not interested in pushing drugs and seeing whether they are tolerated or not, which is the classic model of phase I development. I think our obligation is to understand why an agent is working and selecting the right patients for treatment."

Facilities at Vall d'Hebron now include six labs and a refurbished and expanded oncology department. Baselga says he has strong pathology and diagnostic departments and the key differentiator compared to other translational centres is multidisciplinary integration. It's a far cry from when he started – medical oncology was merely a referral point for chemotherapy. Now every tumour case is discussed in multidisciplinary teams with oncology playing the central role.

A new breast cancer centre will open next year – as he is a breast specialist it is natural that this has been a focus for expansion, but as he points out research is now much more targeting the molecular features of cancer and not its site. "I don't feel restricted to one tumour type. Yes, we do a lot of trials on breast cancer, which is my main area, but also on colon, lung, and head and neck cancers – wherever we see an opportunity we will try and adapt to that disease."

The new breast centre, he adds, will be a "paradigm and laboratory" for future expansion. "If it is successful we will open centres for gastrointestinal, prostate and other cancers – the future for big academic hospitals is to create tumour-focused multidisciplinary teams." Breast is a good place to start, he says, as many patients need chemotherapy prior to surgery, and pathologists, radiologists and genetic counsellors are all also involved – "So it is obvious we all have to work together." (And, pragmatically, it is also a cancer with a strong advocate community and fundraising potential, he notes.)

If all this sounds like a smooth progression, Baselga notes that in the early days many basic problems had to be sorted out. They included convincing the hospital to upgrade the oncology facilities from one of the worst to among the best; being open with patients about their condition, and not allowing families and consultants to hide the truth; and abolishing waiting lists (no mean feat given there are 3,000 new patients visits each year and 30,000 follow-ups).

Another issue familiar to many around Europe has been persuading surgeons to specialise only in particular tumours – that's been agreed at Vall d'Hebron, but is not the case yet in outlying hospitals in Catalonia.

Motivating the medical oncology staff has also not been easy. "For example, I've had to force people to learn English so they can travel and participate in international forums, and internal sessions are also conducted in the cancer community's lingua franca." Baselga is a great advocate of networking and personal bonding with European colleagues. With funding from a Spanish bank he's also inviting experts to come to Barcelona to give talks, but is equally keen that staff get to know them over lunch and dinner.

It's part of his drive to make the most of opportunities for co-operation within Europe. Outside of individual centres, Europeans can often organise trials on large patient populations much quicker than counterparts in the US

> "It's easier to do research in a public health system, and Spaniards are interested in participating"

– studies on adjuvant Herceptin being a case in point, he notes. But the agenda for medical oncology is much broader and more challenging.

The community needs to lobby for medical oncology to be recognised across Europe as a key discipline, feels Baselga – medical oncologists must be the pivotal players in multidisciplinary teams. As he points out, only doctors with a background in internal medicine can hope to understand the molecular basis of cancer and in what combinations, settings and population groups to administer treatment. "The quality of cancer care relates directly to the strength of medical oncology in any centre – there's no question of that. If you look around Europe, there is a tremendous imbalance of quality of care – because we don't have a strong speciality."

It is an opposite view from the one sometimes heard from surgeons – that medical oncology has become very powerful because it gets so heavily funded by pharmaceutical companies. ESMO (the European Society for Medical Oncology), they argue, already has one of the biggest European meetings. "But compare ESMO to ASCO [the American Society of Clinical Oncology], which has 28,000 attendees at its conference – and just look at how many presentations they have from Europe. I love ASCO – it's been fundamental to my career, it gave me a young investigator award, a career development award, and I'm a board member, but we are not doing our job here if most of our major papers go to them."

It may surprise some to learn that ASCO has grown from about 15 employees to close on 300 since 1996 (and Baselga recalls that when it was small he once got a call from the executive director chasing him for a grant application). Those days are long gone. "Now ASCO has tremendous lobbying power and capacity to produce educational materials, and is funding career development – as well as running a great journal and annual meeting. Given that Europe has twice the population of the US, we should have a society of at least the same size and influence as ASCO, especially to bring on the new generation of medical oncologists." The good news, he adds, is that ASCO does also operate as a global organisation, and would be "very happy to help the European cancer community".

Training of oncologists is an especially important topic for Baselga, who is currently chair of ESMO's young medical oncologists working group. Just as cancer care is far from uniform across Europe, training also varies greatly, which can only delay the establishment of medical oncology as a specialism and the emergence of oncology leaders – of whom there is a dearth, according to Baselga. "Are we taking care of our young doctors and providing enough funding for training? No – but the Americans are." He does currently have an Italian investigator under his wing funded by an ESMO award – "She is a superb oncologist" – but there are few such positions in Europe.

So what other kind of changes does he envisage? "I don't want another ASCO – let's play to our strengths and be the champions of multidisciplinary work. The European Breast Cancer Conference is a good model for a meeting, at least. We currently have two journals in Europe – the *European Journal of Cancer* and the *Annals of Oncology* – we should instead have one strong publication to rival the American *Journal of Clinical Oncology* [JCO]. The careers of young oncologists depend on publication, so I can't fault them for sending papers to JCO – they have to look after themselves."

Lobbying at European and national level will be critical to addressing resourcing gaps – and Baselga isn't alone in wanting a professional lob-

"The quality of cancer care relates directly to the strength of medical oncology in any centre"

Speaking at a conference attended by Spain's Queen Sofia at the Real Academia de Medecina in Barcelona, October 2004

bying and fundraising operation. "We need minimum standards for cancer care agreed by law and to create a European movement against cancer." In Catalonia, Baselga is playing his part – dinner with the president of the region helped cement 12 million euros for his new research laboratories, and he's a regular on TV, including a 'telethon' fundraising programme that involved patients speaking up about their treatment. He has also set up a research foundation (Fundació Privada d'Estudis i Recerca Oncològica – FERO), through which the breast centre and a new head and neck cancer lab are being funded, and he hopes to set up scholarships and young investigator awards.

Medical oncologists also need to speak out more about their achievements. Baselga often talks of breakthroughs in clinical research – again, this is something to learn from the US. "There is a psychological issue here with the way medical oncologists communicate – we are making breakthroughs all the time. Breast cancer mortality is dropping 2–3% a year. Colon cancer response rates used to be 12–15% with available chemotherapy – and now with new agents the response to metastatic disease is 84%. Herceptin increases survival of HER2 positive breast cancer by 45%. If these aren't breakthroughs, what are?"

Americans are rather more gung ho. "The Breast Cancer Foundation has a powerful logo, the MD Anderson Cancer Center's logo is 'Making Cancer History'. Memorial Sloan-Kettering says it has the 'best cancer care anywhere'." That's the kind of branding he'd like to see more widely applied, and with the "phenomenal progress" being made with the many new compounds he's involved with, there is no shortage of achievements to trumpet.

With so much to work on he's probably glad of the distractions of home life. He's now a father of four children aged 12 and under – and they sound like an outward bound family; "My wife and I are mad on skiing, hiking and biking." Family life should keep him in Barcelona for the foreseeable future – but he gets plenty of big job offers from other cancer centres, especially in the US, who want the best person to lead their clinical research, so the attractions of Europe may not be enough to keep him for ever.

When he's not reading medical papers, Baselga likes to pursue his keen interest in modern history. One senses that, at just 45, Baselga has every chance of making a history of his own.

They could be alive today

Anna Wagstaff

Every year thousands of people die unnecessarily from cancer because their care is sub-optimal or arrives too late. Europe has known where the problems are for more than a decade and has the knowledge to improve matters. It is the political will that is lacking.

During the 1990s, a series of reports emanating from the EuroCare project revealed significant differences between survival rates for a wide variety of cancers in European countries.

Five years after being diagnosed, a stomach cancer patient in Iceland was around three times more likely to be alive than a similar patient in Slovakia, the UK, Denmark, or Poland. The differences were not just about resources, because Denmark and the UK are relatively affluent with access to the latest drugs and up to date equipment. Many factors may have skewed the results, but it was hard to avoid the conclusion that some patients were dying because their cancer care was not up to scratch.

The EuroCare statistics shocked the UK into overhauling cancer services, with an emphasis on reducing waiting times and ensuring equal access to specialist care. Denmark also took measures to improve the quality of its cancer care.

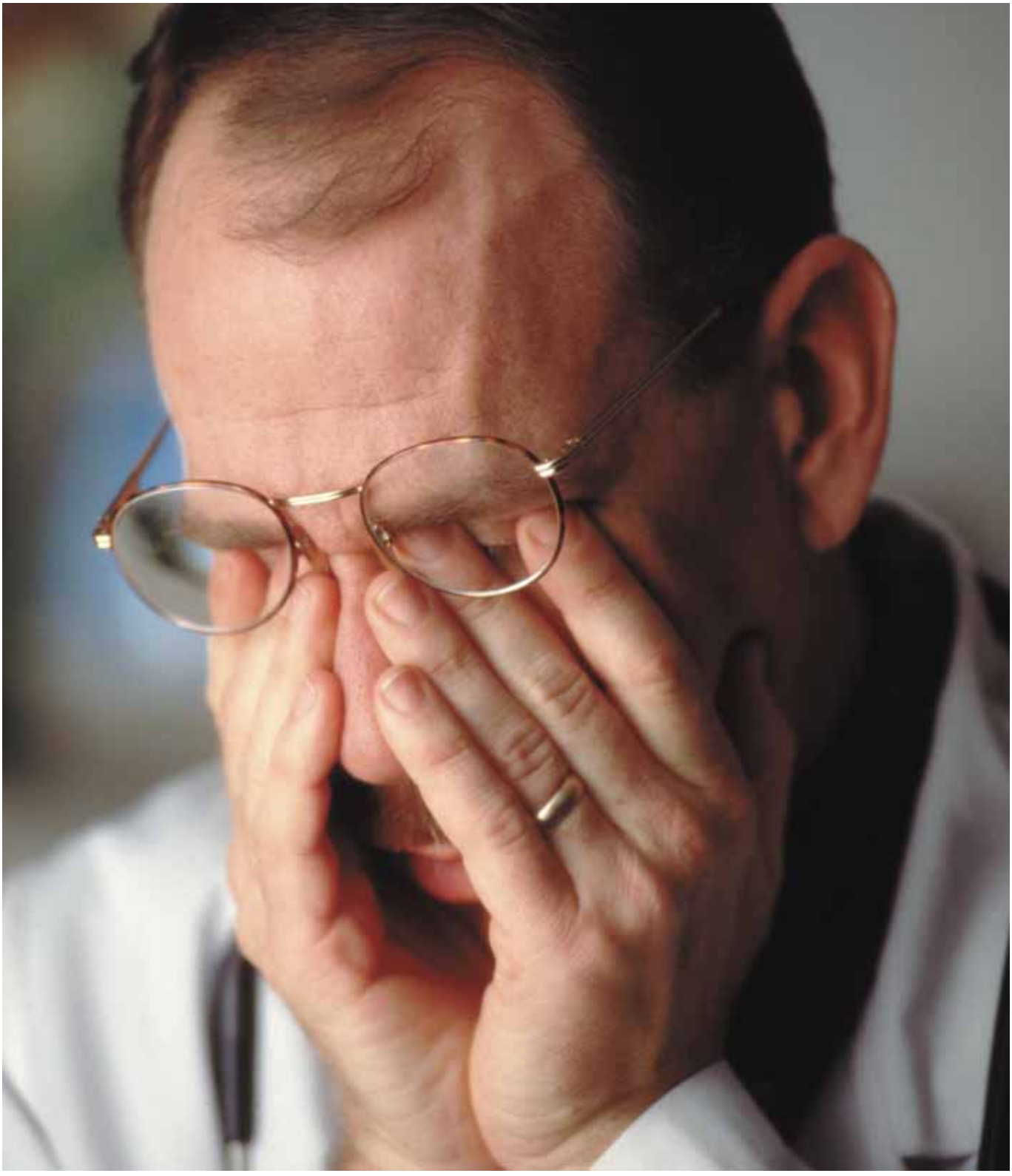
Many lessons were learnt. But there is plenty of evidence to show that patients are continuing to die across Europe because available knowledge and techniques are not being used to best effect. Indeed, some experts believe that the situation is likely to get worse.

Know your disease

Oncologists need to know an increasing amount about the pathology of the disease. If the tumour has been incorrectly defined or wrongly staged, the treatment will be sub-optimal. Guiseppe Viale, professor of pathology at the University of Milan – European Institute of Oncology (EIO), believes that most oncologists would be horrified to know how frequently this happens.

Take breast cancer. Pathologists were once simply required to define the extent and type of tumour through examining its morphology; today, they have to characterise the cancer in far greater detail. They report on how many lymph nodes are involved and evaluate the tumour for oestrogen, progesterone and HER2 expression. On the basis of these reports, fundamental decisions are made such as whether the patient requires adjuvant chemo- and/or radiotherapy, whether hormonal therapy is sufficient, or whether the patient can safely forego adjuvant therapy following surgery.

Viale says that confidence in these reports is often misplaced. "We know that 20–25% of patients who have been assessed as node-negative have disease recurrence and will



JOSE LUIS PELAEZ, INC. / CORBIS / CONTRASTO

eventually die of the disease. If we go back to those regional lymph nodes and examine more sections, we will find metastases in the large majority of these patients. The risk to these patients was not assessed correctly in the beginning."

The story on endocrine response status is hardly more encouraging. Quality control in the UK has established that the false-negative result for oestrogen and progesterone receptors lies somewhere between 15% and 25%; the picture in Germany is a little better (11–24%). Many European countries have no quality control procedures, and the results coming out of their labs could be even more unreliable. Viale estimates the false-negative figures in Italy to be closer to 20–25%.

There are also problems with HER2 evaluation. False-positive rates of up to 30% are common and this is true whether the assay is done by immunohistochemistry or using the FISH (phosphorescence in situ) procedure. The problem, says Viale, lies with the pathologist rather than the test.

"You can see that a large fraction of breast cancer patients are not treated properly… it makes you a bit nervous about what is happening around you."

Problems are more evident in breast cancer, because we know more about subtypes and the implications for treatment than for many other cancers. But differentiation and tailored treatment is the future for most cancers, giving the role of the pathology labs even greater importance.

Viale believes that pathologists who are not working as part of a multidisciplinary team are not aware of how their conclusions determine treatment.

This is something Viale himself learnt only after he left his job in a general hospital. "I thought I knew breast cancer, but when I started working at the EIO, I changed my approach completely. I started to realise, for instance, that saying '10% progesterone positive' is completely different to saying '80% positive' in terms of treatment – it's not just a question of saying 'negative' or 'positive'. Once you realise that, you are ready to spend the necessary time to make an accurate evaluation."

One way to help pathologists become more aware of the significance of their role would be to make funding available for pathologists from centres participating in clinical trials to attend coordinating meetings. They should also receive feedback on the quality of their evaluations in real time, rather than several years later after the trial has closed.

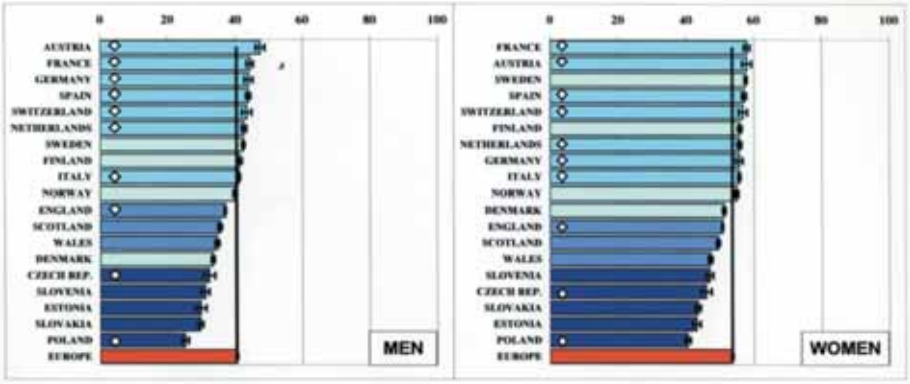
In some countries poor access to the latest diagnostic and imaging techniques is an obstacle to accurately defining the disease.

Adrian Udrea, who works in the chemotherapy department at the Oncological Institute of Cluj, Romania, says that the standard of medical oncology training is very similar to that in Western Europe and that money is available for cancer drugs. However, clinicians cannot always treat patients effectively because they are unable to characterise the disease.

There are no immunohistochemistry testing facilities outside the main cancer centres in Bucharest and Cluj, and these centres do not offer services to smaller hospitals. Access to imaging techniques such as bone scan, CT and MRI is also extremely limited. The ultrasound equipment is 20 years old, and unreliable.

"There must be some way to organise the system to work better with the money we have," says Udrea. "We are spending money for expensive drugs, but we don't know what we need to know in order to use them effectively."

The problem is not confined to central and eastern European countries. In Italy, for instance, though costly trastuzumab prescriptions are reimbursed by the national health system, the HER2 test that indicates whether the tumour might respond to the drug is not.



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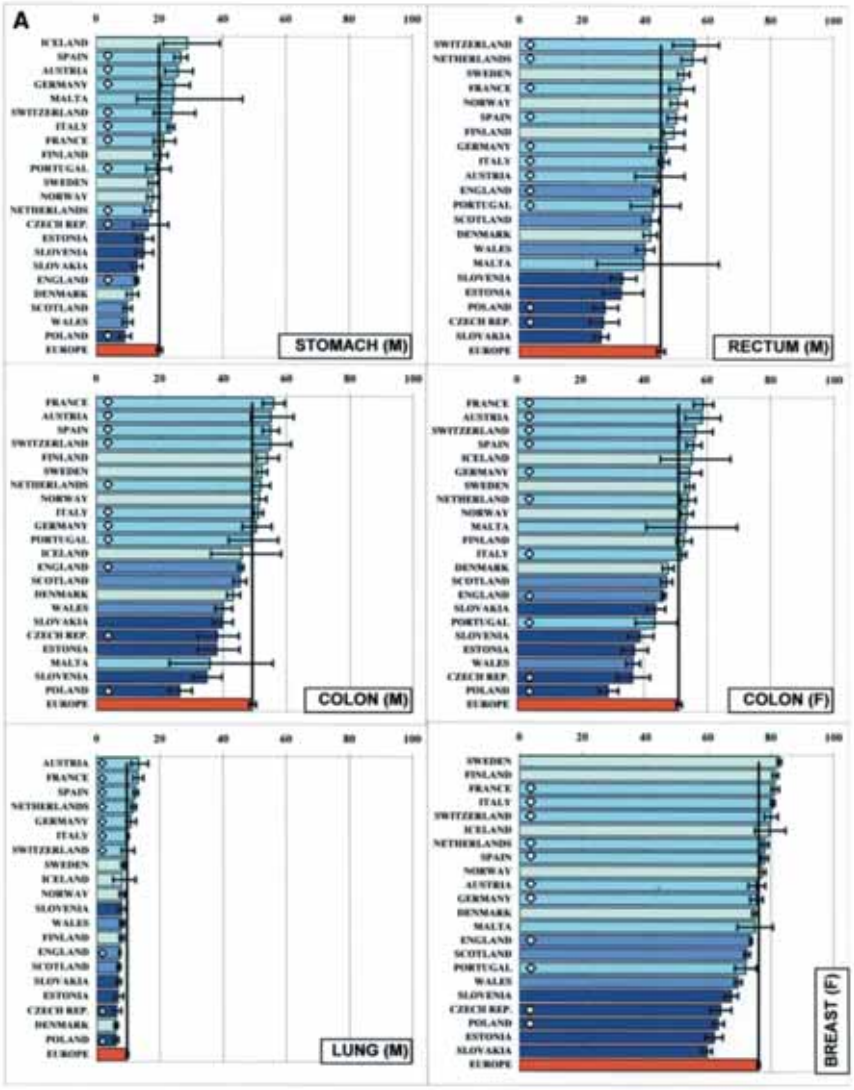


Comparative index of 5-year relative survival (%) by country for adults diagnosed in the period 1990–1994, followed up to 1999. These were the graphs that shamed the UK into improving cancer services

Know your procedure

Surgery

Since the 1980s, studies have shown that referring a patient to a specialist centre for difficult procedures to excise pancreatic, gastric and rectal cancers significantly lowers their risk of dying from postoperative complications. The latest figures from the Netherlands show patients operated for pancreatic cancer in small hospitals are ten times more likely to die than those treated in the larger centres.

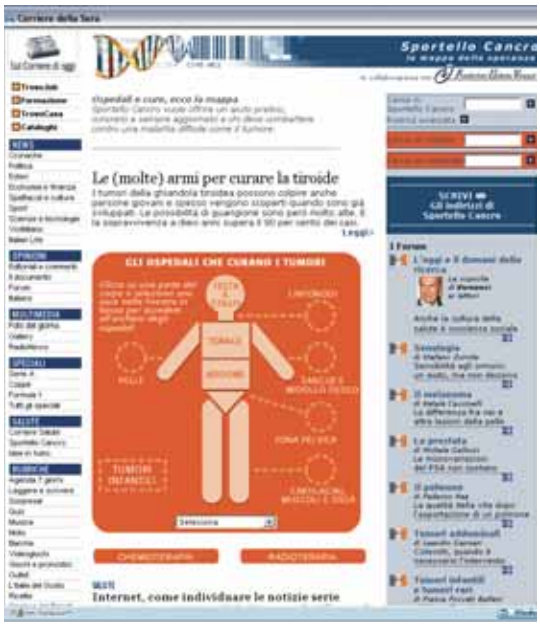
Expert surgery is also associated with far lower local recurrence rates – between five and ten times lower in the case of rectal surgery.

Lex Eggermont, head of surgical oncology at the Erasmus University Medical Centre in Rotterdam, says observing simple principles will minimise unnecessary deaths from poor surgery. "First you must be well trained. Second, there is a direct volume effect – the more you do, the better you are. If you don't do more than 15 rectal or 15 oesophageal or 15 pancreatic or 15 gastric cancers a year, you shouldn't do any at all, because you are automatically associated with worse outcomes."

This principle has been recognised in Europe for 20 years, and many countries encourage regional or national specialisation – but bad practice still continues. Eggermont says that there is a need for a new referral culture, where different units work collaboratively rather than competing for patients, and agree a rational way to divide specialist services.

Even in the Netherlands, with its excellent referral culture and commitment to regional specialisation, it is proving hard to stop a few errant small hospitals carrying out low volumes of oesophageal or pancreatic operations. The situation is probably far worse in other countries, particularly those with weaker public health sectors and poorly coordinated cancer treatment delivery, and in poorer and more rural areas.

The public have little access to information about volume. However, www.corriere.it/sportello-cancro, a website supported by the leading Italian daily the *Corriere della Sera* and the Umberto Veronesi Foundation, provides a fascinating insight into how surgical procedures are divided



The Italian website www.corriere.it/sportello-cancro. For the best chance of survival, click the relevant part of the body to find out which hospitals in your region have the greatest experience in dealing with your type of cancer – and which hospitals to avoid

between major centres and peripheral hospitals across Italy. It shows that around 230 hospitals are carrying out surgical procedures for cancers of the digestive tract even though their annual case load is less than the recommended 15. When the figures are broken down to surgery on the oesophagus or rectum, the number of hospitals carrying out between 1 and 15 procedures is very much higher.

Radiotherapy

Of all cancer treatments, radiotherapy is the easiest to systematise. It is concentrated in larger centres, with fewer problems associated with low volumes of treatment. Decades of quality control prevents most easily identifiable mistakes, but controversy remains over long-term effects. Radiation for testicular cancer has been associated with new cancers up to 20 years later and there is some evidence to show that high-dose radiotherapy to treat Hodgkin's lymphoma or breast cancer can damage the heart.

Intensity modulated radiotherapy allows for more aggressive and effective treatment, concentrating firepower on the tumour and sparing normal tissue to a greater extent. However, if mistakes are made, the damage can be all the greater. Jacques Bernier of the Oncology Institute of Southern Switzerland in Bellinzona, says, "We have to have much stricter controls before irradiating, because if the plan calculation and the delivery don't correspond, you can give two, three or four times the dose you calculated."

Gross errors are rare however. One UK study of almost 2000 patients treated with 95,000 individual doses showed an error rate of 0.18%, all of minor clinical significance.

Of greater concern, is the under-investment in latest equipment and software, leading to increased waiting time or treatment using outdated methods. Radiotherapy now forms a part of the treatment of more than 50% of all cancer patients, but according to the European Society for Therapeutic Radiology and Oncology (ESTRO), the services in many countries cannot cope with this level of demand, and access to treatment is now a major problem.

Know your patient

Medical oncology has emerged as the defining mode of treatment for most cancers and the arena in which major advances are expected. Unfortunately, it is also least amenable to quality control.

In the 1980s and '90s, huge variations in the way patients were being treated led to much greater emphasis on evidence-based medicine. The idea was to educate all oncologists to act according to the best available evidence rather than relying on empirical knowledge or on the established policy in their departments.

Recently published studies show that following guidelines has an impact on survival. However, the key to success lies in how guidelines and evidence is applied to each patient.

Aron Goldhirsch of the Department of Medicine at the European Institute of Oncology, worries that too many medical oncologists use guidelines uncritically and prescriptively.

"Every patient is absolutely unique, but part of a population. Statistics and epidemiology have brought medicine away from individual patients, so that what is said is actually 'on average'. It's like 'one-size-fits-all'. If we don't recognise patterns of diversity from one individual to another, and we take an average answer as a good answer for everyone, we are likely sometimes to be wrong."

Statistics in cancer medicine is typically used to group people into wider populations in order to analyse outcome and factors that influence response to treatment. Goldhirsch's concern is that no-one is teaching the methodology of applying those statistics to the individual patient.

Goldhirsch is involved in the MINDACT breast cancer trial (MIcro-array for Node negative Disease may Avoid ChemoTherapy), which seeks to find out how responses to therapies vary according to the

specific genetic and pathologic characteristics of subgroups of node negative breast cancer.

He says that, while breast cancer is ahead of the field in defining subtypes and identifying oncogenes, the same process is now happening elsewhere, and all cancers will require ever more precise treatments. The trouble is that as much of the evidence that oncologists currently use represents only an average response, some tumour subgroups will respond better than the average, and others may not respond at all.

A wise oncologist, says Goldhirsch, does not apply evidence unquestioningly, especially when detailed information is not available. 'Average' data are just not precise enough. "Doubt is very important. When you don't have anything else, evidence-based is by far the best, but you must use it critically or you end up stagnating knowledge."

Encouraging oncology departments to participate in well-structured clinical trials that apply tailored treatments, would be one of the most effective ways to improve their methodological approach, he says.

Bob Pinedo, director of the VUmc Cancer Centre at Vreie Universiteit hospital in Amsterdam, emphasises the diversity of patients, as well as the diversity of tumour types and believes that young oncologists need more training in internal medicine to allow them to tailor treatment to their patient.

Medical oncologists give toxic drugs to people who may not only be weakened by cancer, but have co-morbidities such as heart conditions or diabetes. They may be taking other medicines and their organs may not be functioning normally. Pinedo feels young oncologists are not being taught to take this into account when they prescribe medication, and some patients are being put at risk as a result. "You need to know what is going on with the patient. You need to do a lot of research making use of their tissues and blood to understand the biology, to understand their pharmacodynamics. It's not just a question of measuring drugs, you need to know the effects of your drugs on the organs."

Knowing your patient also means knowing who is at extra risk of cancer. Pinedo is frustrated at lack of effective monitoring for people known to be at very high risk.

He wants to see women who have a family history of BRCA positive breast cancer routinely screened by MRI, to detect disease earlier than by mammography.

People with familial colon cancer also need more effective screening he says. Studies coming out of the US and the Netherlands have shown that only half of the patients in whom adenomatous polyps had been indentified by colonoscopy show positive for colon cancer using the faecal occult blood (FOB) test. So why, asks Pinedo, are we still relying on this method of detection for people known to be at high risk? "I foresee a big problem here. We will get angry people who have been screened with the FOB test and they get cancer, and they will say why did this happen?"

Multidisciplinary treatment

Top quality pathology, medical oncology, surgery and radiotherapy are all essential to save every patient who can be saved. But each mode of treatment becomes significantly more effective in the presence of the vital ingredient: multidisciplinary collaboration.

The majority of treatments involve two or three types of therapy, often interlinked. Almost 90% of all radiotherapy now takes place within a multidisciplinary framework.

Effective multidisciplinary working makes it possible to select the most effective treatments with the least damage to the patient. Supportive care is also essential. Nutrition, for instance, can make the difference between surviving or dying for very ill patients. Monitoring and dealing promptly with life-threatening side-effects such as thrombocytopaenia and neutropaenia is essential; the involvement of expert cancer nurses in the multidisciplinary teams can make a difference here.

Such a multidisciplinary approach is impractical outside of larger hospitals or networks of collaborating centres. Where cancer patients make up only a small proportion of a surgeon's or pathologist's work, they will not be able to organise their timetables around multidisciplinary meetings, which would in any event happen too infrequently for them to build a relationship or to understand the roles and problems of other specialists.

It is the combination of specialist surgery and multidisciplinary working that has been credited with significant differences in survival rates

If we don't recognise patterns of diversity from one individual to another, we will make mistakes

Involving pathologists, cancer nurses and dieticians in the team can make a difference to survival

between larger centres and peripheral hospitals in a number of studies, notably in Scotland in the early 1990s. Finding a way to deliver specialist multidisciplinary treatment to all patients, no matter where they live, is one of the logistical challenges for good cancer care.

Teaching cancer

Decades after the multidisciplinary approach was recognised as effective, it is still rarely taught as a concept in medical schools.

Franco Cavalli of the Oncology Institute of Southern Switzerland, Bellinzona, says the fragmented way in which cancer is taught lies at the heart of many problems. "There is no overall teaching in oncology. You will have the internist, who will talk a little bit about cancer, the surgeon, who will talk a little bit about cancer, the pathologist and so on. Most universities do not have well-structured teaching on cancer, and because of that most physicians, when they finish their training, do not know enough about cancer."

Waiting to die

The best cancer services are undermined if patients do not receive a diagnosis and treatment when they need it. Evidence shows that in some tumours, making patients wait weeks, sometimes months, for radiotherapy reduces their chance of a cure, allowing the tumour to grow beyond a 'curative size' or to metastasise. ESTRO, the professional body for European radiologists and radiotherapists, says very few EU countries have sufficient linear accelerators and trained staff to provide an adequate service, and that a high proportion of patients are treated outside clinically acceptable time limits.

Where waiting lists are long, radiotherapy departments systematically treat patients when they know it is too late, and doctors have to choose which patient will receive the best care today, and which will have to wait – or be assigned to palliative treatment simply because their chance of a cure is below the threshold that makes them a priority within an overstretched system.

Pinedo believes there is also a critical shortage of oncology specialists across Europe that will become more acute as more patients survive longer. "We know that the prognosis for colorectal cancer improves if you do secondary surgery. But if you have a waiting list of months for a primary colon cancer, you are not going to take a patient with a little metastasis and put them on the list." Pinedo still goes to multidisciplinary meetings and argues for that surgery to be done, but he is aware of the pressure. "You know the surgeon is already very upset because of his waiting list. I know I'm asking them something I shouldn't ask, because there are certain things you just cannot ask these days, even though you know it is the best for the patient."

He worries that the medical profession seems to accept delays as a fact of life. "If 30 years ago you would say, 'operate within four weeks', now you accept an operation within eight weeks. I just cannot work that way. I find it horrible, because we don't tell our patients the risks."

What next?

All over Europe, patients who could have been saved are dying because they did not get high-quality treatment when they needed it. We know a lot about the training and systems of care delivery needed to avoid unnecessary deaths. We need now to know how to get there from here.

Patient power

Many argue that patients hold the key, through exercising informed choice over where they are treated.

Eggermont says the most effective thing to do is "bombard" patients with advice to ask their hospital the crucial questions: "How often are these procedures performed here? What is your track record? What are your mortality figures?" And if the answer is not reassuring, they should go elsewhere.

Patient groups have been advocating this approach for years, but they have precious little information to go on; the Sportello Cancro website is an exception. Eggermont would like to see similar statistics on volume and track record available in all countries. "That would force the system to reform."

In the Netherlands, the Breast Cancer Patients Association is setting its own agenda. It has drawn up quality guidelines, covering issues such as waiting lists, expertise and choices between different interventions, and

has set a deadline of January 1 2007 for treatment centres to comply or face a boycott by patients.

A Europe-wide accreditation system for specialist breast cancer units, developed and operated by the European Society of Mastology, is in the pipeline. This will set standards for specialist centres in breast cancer care, and will offer an important marker for patients deciding where to go for treatment.

But directing patients to the best treatment centres creates its own waiting list problems. Patients may have to choose between waiting eight weeks for top-quality treatment, or immediate treatment at a hospital with less expertise. In the end, says Pinedo, pressure on centres of excellence can compromise the quality of care they can offer.

The European Court of Justice believes that patients should be able to use their power. In three landmark cases between 1998 and 2003, it ruled that patients have the right to be reimbursed for treatment in another Member State if they cannot get the treatment they need from their own health system within a reasonable time.

This is not a solution, since it does not create any new resources in the offending state, but it establishes the legal principle that timely treatment is a right that health services cannot ignore.

Plan ahead

In the end, the answer lies in networks of adequately resourced centres that can provide all sectors of the population with access to specialist facilities. This is the system that has kept Sweden, Finland and the Netherlands at the top of the cancer survival league. It is now being emulated by countries like the UK, Ireland and France, which can build on a strong base of 20 regional cancer centres.

Building new state of the art cancer centres is not always the issue. The Netherlands, for instance, is developing a structure designed to achieve top-quality treatment in smaller hospitals that agree to specialise and coordinate their work. It does, however, require a system in which there is no big financial loss in referring a patient elsewhere. It is also easier in more concentrated populations, although Sweden pioneered this system, and distances there can be great.

The French national cancer plan, introduced in 2003, represents a welcome attempt to address all aspects of cancer care: training and continual medical education, equal access, a mandatory multidisciplinary approach and patient information. Importantly, it also supports the work of the French cancer registries, which should provide information that can be used to further improve the system.

Despite these encouraging signs, Cavalli cautions that France has always believed in a strong state, and is probably an exception. He argues that the current European economic and political climate is driving the organisation of public services towards greater liberalisation, which may be counterproductive since cancer care needs well-planned systems driven by collaboration not competition. If, for instance, hospitals are obliged to contract out specialist pathology services, there is no way that pathologists will be able to work within a multidisciplinary team.

Health budgets are generally static or shrinking, because of pressure to limit public spending. He says there is a danger of developing the two-tier health system that exists in the US – a highly sophisticated system for those who can afford it, and a fundamentally inadequate one for those who cannot.

Cavalli points out that life expectancy in Russia has decreased by around seven years since the collapse of state-led systems, some of which can be attributed to the collapse of the health system. He says there is no reason to believe that minimising the public sector and encouraging private provision in eastern Europe will provide an effective cancer service for more than a tiny part of the population.

Monitor the system

Funding for the EuroCare project has dried up, and as a result many national or regional registries have lost their sense of dynamism and purpose. Many registers have also been hit by privacy legislation, though some people argue this is more of a problem of political will or legal interpretation.

Jan Willem Coebergh, of the Eindhoven Cancer Registry in the Netherlands, says he is worried by this apparent retreat from the approach that taught us much of what we now know about unnecessary can-

Very few EU countries are able to provide an adequate radiotherapy service

cer deaths. His concern is that, without effective registries, we will no longer be able to tell which systems or procedures are working and which are not. Ian Kunkler, who analysed registries for the Scottish cancer plan, agrees. "A cancer service without cancer registration is like a clinical trial without a statistician."

Norway is swimming against the tide. The government is investing heavily in upgrading its registry system to include detailed pathological and clinical data. Surgical procedures, radiotherapy and medical treatment will be recorded as well as instances of recurrences and metastases. This huge project requires close cooperation between registries and clinicians, but the government is convinced that the information it yields about variations in survival will be worth it.

But there is also plenty that could be learnt from less ambitious projects that analyse smaller populations. The European Network of Cancer Registries has recently regrouped and is looking to promote these sorts of studies throughout Europe.

Winning the argument

People will continue to die from cancer under any system. However, dying because your health system let you down, you live in the wrong country or even in the wrong part of the country, is not inevitable and should be considered unacceptable.

When the compelling voice of patients and their families joins with the medical profession and is backed by firm evidence, it is possible to capture the media and political agenda. That is what is needed to force governments to address the inequities revealed by the EuroCare data, and ensure that every cancer patient is given the best chance of life.

10 ways to prevent unnecessary deaths

1 **Training.** Teach oncology in a holistic way instead of splitting it between disciplines and organ specialties. Teach the importance of early detection, multidisciplinary treatment and comorbidity issues.

2 **Pathology.** Raise awareness among pathologists of the key role they play. Involve pathologists in planning and executing clinical trials. Introduce greater quality control, and feedback results quickly.

3 **Surgery.** Ensure that surgeons carrying out complex procedures do at least 15 such cases a year. Make relevant information available on the Internet and encourage patients to choose carefully where they go for treatment.

4 **Radiotherapy.** Ensure rigorous quality control of high-dose modern procedures. Conduct long-term studies to monitor possible late side-effects such as heart problems in breast cancer and Hodgkin's patients, or new tumours that may emerge decades after treatment.

5 **Medical oncology.** Promote the use of evidence-based guidelines and encourage oncology departments to participate in trials. Improve training in interpreting statistical evidence to tailor treatment to individual patients.

6 **Multidisciplinary working.** Ensure that all cancer treatment takes place within a multidisciplinary setting, either within one hospital or by co-ordinating specialists from different hospitals.

7 **Networks.** Organise well-structured networks of specialist centres. Encourage a culture of referral where hospitals collaborate rather than compete for patients.

8 **Registries.** Monitor effectiveness by collating and analysing data on diagnosis, treatment and survival.

9 **Waiting time.** Delays can cost lives. Define acceptable time frames for imaging, pathology and specialist treatment of different cancers, and provide sufficient resources and effective systems to keep delays within those limits. Educate patients to demand treatment within that time frame.

10 **Cancer plans.** Organise national and regional cancer plans, covering training, resource allocation, location of specialist services, professional guidelines, quality control, and evaluation.

What do animal experiments really tell us?

Robert Matthews*

Do animal models reliably predict toxic effects in humans, or are they actually blocking development of vital new drugs? Two recent major health scares have reignited the old debate.

Two huge industries affecting the lives of millions are currently in the midst of major health alerts. Concern over serious side-effects have cast a long shadow over promising new painkillers developed by the pharmaceutical industry known as COX-2 inhibitors. Evidence linking the drugs to an increased risk of heart attacks led the US giant Merck to voluntarily withdraw its version, known as Vioxx, from the market last September, and an investigation by the US Food and Drug Administration (FDA) raised concern about similar drugs.

Then in February it was the turn of the UK food industry, with the discovery of traces of a banned dye known as Sudan I in a sauce made by Premier Foods, a leading UK supplier. In the ensuing health alert, the UK Food Standards Agency (FSA) found that hundreds of products had been inadvertently contaminated by the dye, which has been linked to cancer.

As the initial furore starts to fade, both these health scares are being seen primarily as wake-up calls to both industry and regulators about the monitoring of product safety.

In the case of COX-2 inhibitors, the FDA is allowing some to remain on the market – albeit with much sterner safety warnings to protect those most at risk from side-effects. Meanwhile, while shops and supermarkets in the UK hunt down produce contaminated with Sudan I, the FSA has continued to stress that the risks involved are "very small".

As well it might, for it is now clear that the scientific case against Sudan I is far from compelling. Laboratory safety tests involved feeding rodents with levels of Sudan I equivalent to human consumption of the sauce that triggered the scare at a rate of three tonnes a day for two years. Even after such gargantuan exposure, the animals failed to produce consistent evidence of a cancer risk. Other tests hinted at links with bladder and liver tumours – but only after the dye was injected directly into the organs of laboratory animals. While the scientific basis for both the Sudan I and COX-2 inhibitor health scares may be contentious, they have highlighted the need for close surveillance and prompt action if problems emerge. At the same time, however, an even more fundamental question has gone begging: just how reliable are animal tests of product safety?

In the case of food safety, the relevance to humans of animal tests involving colossal intakes or direct injection into organs is clearly questionable. The use of animals in drug safety testing raises altogether more complex issues, however – as the COX-2 painkillers controversy shows.

In line with standard practice, Vioxx and the other drugs were tested in at least two different types of animal before entering clinical trials with humans. One of the key aims of such "pre-clinical" testing is to detect signs of serious side-effects. In the case of the COX-2 drugs, the animal testing failed to warn of the cardiovascular effects that have prompted the current furore. Indeed, several animal studies suggested the drugs would actually reduce the risk of such side-effects.

So what went wrong? Antivivisectionists have been quick to voice their standard objection: animals are not humans. For all its familiarity, it is an argument that does have relevance to COX-2 inhibitors like Vioxx. In 2000, barely a year after the launch of Vioxx, a study of over 8,000 patients suggested that those taking the drug faced a significantly

STEVE CHENN / CORBIS / CONTRASTO

Animal tests may be blocking the development of many safe and effective treatments

increased risk of heart attack. Yet subsequent animal-based research continued to suggest such drugs could reduce the risk – prompting even Merck's own experts to concede in the *American Heart Journal* that "The relevance of these animal models in predicting effects in humans is uncertain."

It is becoming clear that such uncertainty extends far beyond one class of blockbuster drug. The leading journal *Nature Reviews: Drug Discovery* last year published a review of the evidence that animals are reliable predictors of toxic effects in humans. The authors found that the evidence was "fragmentary", with the few published studies pointing to "significant over- and under-prediction of adverse effects from animal studies that varies with the particular organ or system."

The review also highlighted the lack of basic data needed for a scientific assessment of animal testing, such as measures of predictive power and their statistical significance.

As it stands, the evidence suggest animal tests may be unduly sensitive,

ED KASHI / CORBIS / CONTRASTO

The animal testing failed to warn of the cardiovascular effects that have prompted the current furore

wrongly predicting toxicity in compounds that are in fact harmless to humans. If so, it would be an ironic twist to the widely-held belief that tests of animal are crucial to the advancement of medicine, as they may in fact be blocking the development of many safe and effective new treatments.

Yet in the absence of large-scale studies comparing drug responses in animals and humans, it is impossible to know. Supporters and critics of animal testing continue to trade anecdotes of individual successes and failures, more systematic studies typically being so small they lack statistical credibility. In another irony, the drive to minimise the use of animals has compelled researchers to draw huge conclusions from meagre evidence. For example, the studies designed to probe the effect of COX-2 inhibitors on cardiovascular risk typically involved fewer than 20 mice. The authors of last year's review called on both regulatory bodies and drugs companies to publish data currently languishing in their files. Whether the outcome will confirm or confound the view that animals usefully predict human reactions remains to be seen. What is clear is that, given the current paucity of systematic evidence, it is not necessary to be a placard-waving protestor to harbour doubts about the validity of animal testing.

DETECTING NASTY EFFECTS IS (MUCH) HARDER THAN IT SEEMS

The health scares over COX-2 drugs and the food dye Sudan I have highlighted the challenge of assessing health risks from limited data. While studies involving huge numbers of patients or laboratory animals are clearly better at detecting side-effects than small ones, they are also far more expensive and time-consuming. Worse, the ability of a study to detect risk does not increase pro-rata with size: to double the sensitivity, the required number of patients quadruples.

Worst of all, estimating the required numbers demands some guesstimate for the likely level of risk – and a bad guess raises the danger of the study being "underpowered", lacking the numbers needed to detect the true level of risk.

One solution is to set up a trial so large that it is sure to have a reasonable chance of detecting serious side-effects in one patient out of every *N* taking the drug. Statistical theory then shows that a comparison of 4 times *N*-squared patients taking the drug with the same number taking a placebo will do the trick. The bad news is that for blockbuster drugs like Vioxx, side-effects affecting just 1 in 1,000 patients constitute a major health alert – and detecting that level of risk demands a study involving millions of people. The only way of acquiring such vast numbers is for pharmaceutical companies and regulators to keep drugs under close surveillance long after approval.

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Tackling cancer: the view from Brussels

Interview with Markos Kyprianou

Things seem to have gone quiet at the EC since 2000, when Europe Against Cancer – a concerted programme aimed at reducing cancer deaths by 15% – came to an end. Where is Europe concentrating its cancer effort now? *Cancer World* asked Markos Kyprianou, who took over as Commissioner for Health and Consumer Protection last May.

Europe Against Cancer provided a funding stream for many prevention and public education initiatives. How has the EC's work in these fields been carried out since the programme ended?

MARKOS KYPRIANOU A crucial aspect of the fight against cancer lies in taking forward the European Code Against Cancer. I believe we must continue to send the message of the Code out to EU citizens that many cancers can be prevented. If the citizens follow the Code's commandments, the annual number of death cases from this dreadful group of diseases could be cut by 350,000 within a decade or so. As Health and Consumer Protection Commissioner, I have put the battle against cancer-linked issues such as tobacco among my top priorities. Our new "HELP" campaign against tobacco will invest 72 million euros in helping citizens avoid or give up smoking, which accounts for over 650,000 deaths in the EU each year. In addition to the campaign against tobacco, the Commission is working with Member States to improve cancer control through better information exchange, communicating best practice and supporting actions to improve prevention, detection and treatment of cancer.

What action is likely to be taken on the recommendations contained in the ASPECT Report *Tobacco or Health in the European Union*, with particular regard to research into effective tobacco control policies and ratification of the Framework Convention on Tobacco Control?

MARKOS KYPRIANOU The ASPECT Report has certainly been useful in deciding how the EU should proceed in its campaign against tobacco, and we will continue to take the recommendations on board for future actions. With regard to the Framework Convention on Tobacco Control, which entered into effect at the end of February, over half of the EU Member States have already ratified it, while the EU and remaining Member States are working to do so as soon as possible. Many of the provisions of the Convention are already in place in the EU, such as restrictions

Markos Kyprianou. The first commissioner to come from newly joined Cyprus, Kyprianou worries that many of the new Member States put too little money into healthcare, while they also suffer some of the highest rates of cancer

on tobacco advertising and sponsorship, a ban on misleading tobacco labelling and mandatory health warnings on all tobacco packs.

With regard to research – which is undoubtedly an important aspect of tobacco control – DG Health and Consumer Protection has been working closely with DG Research to negotiate on allocations from the next Research Framework Programme. Health research has been identified as a significant priority. There are many competing priorities in the field of research, and it is not possible to give an individual budget line to every policy issue that we would wish to. However, once the final figures for the Research Programme have been agreed, I would certainly expect that tobacco-related research will receive sufficient funding under the overall health research heading.

How is the Commission monitoring the implementation of recommendations on cancer screening and encouraging Member States to implement them?

MARKOS KYPRIANOU Following the adoption of the Council Recommendation on Screening for Cancer in December 2003, the implementation

COMIC COMPANY

Europe's 10-point Code Against Cancer. This poster was produced in 1997 as part of a UK public health campaign within the framework of the Europe Against Cancer programme. The European Code Against Cancer was updated in 2003, but it is no longer being promoted so effectively

of more effective screening programmes for breast, cervical and colorectal cancer was established as a political priority by the Commission. Member States are currently working to implement these recommendations and improve cancer screening. The Commission lends support to its implementation by the parallel development of better and more comprehensive EU guidelines on best practice in cancer screening. The fourth edition of guidelines for breast cancer and the first edition of guidelines for cervical cancer are expected to be published later this year.

Guidelines for best practice in colorectal cancer screening will have to be developed with the support of the current public health programme 2003–2008. These benchmarks will provide new, improved, population-wide cancer screening guidelines in the EU. We are expecting Member States to submit progress reports on the measures they have taken to improve screening next year. In addition, the new European Cancer Network will have a close look and will come up with proposals to improve the EU guidelines and national screening programmes by about the same time. The Commission will then produce a report on the

"Our new 'HELP' campaign will invest 72 million euros in helping citizens avoid or give up smoking"

"I would expect tobacco-related research to get sufficient funding under the health research heading"

implementation of the cancer screening programmes by 2007.

What can the EC do to foster collaboration between the charities and academic departments across Europe that are leading basic cancer research?

MARKOS KYPRIANOU Although there is no single institution in the EU comparable to the US National Cancer Institute, we do have a number of different instruments through which information is pooled and shared. For example, there are EU-funded networks which bring together cancer experts from all Member States. Through these networks, information can be coordinated and exchanged on cancer prevention, treatment and control. eHealth is another effective tool which uses modern technology to pool information on healthcare, not only from governments and EU policy makers, but also from academics, charities and other stakeholders. In May, I will be attending the 3rd Ministerial meeting on eHealth in Norway, at which we will review this tool and look at how it can enhance health communication and coordination throughout Europe.

How can the EC contribute to reducing disparities between countries, regions and sectors of the population, particularly in early detection and access to quality treatment?

MARKOS KYPRIANOU Undeniably, there are disparities across the EU when it comes to the standard of national healthcare provisions, including cancer treatment. I am concerned, in particular, at the insufficient investment in healthcare in the new Member States, especially as the rate of diseases such as cancer is generally higher in these countries than in the rest of Europe. I would stress that Member States must recognise the absolute necessity of providing adequate resources for their own healthcare systems if EU public health standards are to improve.

This requires the provision of more national funding for healthcare, for example by making health a priority in the use of the European Fund for Regional Development. However, the Commission, for its part, will continue to facilitate closer cooperation between the Member States on healthcare issues, in a way that will support reform and encourage policy development.

Through mechanisms such as the Open Method of Coordination, Member States can exchange information on best practices, compare policies and learn from each others' experiences. Member States are due to present their first statements on challenges they face in healthcare later this year, and from there we can look at the best way to work towards narrowing the gap in standards between Member States. In addition, the Health Programme 2003–2008 will continue to support actions of cancer prevention and control.

With regard to the EU's contribution to the reduction of breast cancer mortality, as requested by the European Parliament in June 2003, there are three measures. Firstly, the Council

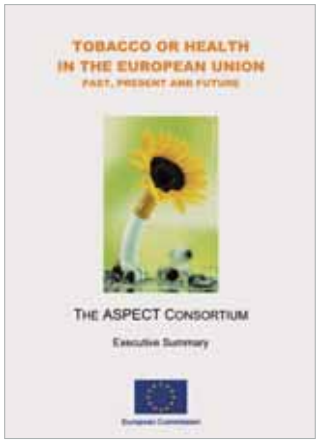
"Effective screening for breast, cervical and colorectal cancer is a priority for the Commission"

Recommendation on cancer screening has been adopted. Secondly, the European Breast Cancer Network's fourth comprehensive guidelines on quality assurance in mammography improves and extends this European benchmark for best practice in mammography to best practice in management and follow-up of screen-detected breast cancer lesions.

Finally, the new European Cancer Network will monitor the developments and come up with recommendations for future improvements. Such measures should certainly assist in reducing the disparities in survival rates across Europe.

What measures is the EC taking to improve, harmonise and analyse the data available on cancer control since support for the EuroCare cancer registries initiative ended?

MARKOS KYPRIANOU EuroCare, financed by several successive EU research programmes, is a nice example of how successful the European Network of Cancer Registries (ENCR) has been with successive funding by Europe Against Cancer. EuroCare was initially hampered by low quality and lack of standardisation and comparability of the basic cancer data. However, the more the ENCR improved the standards and comparability of the seven basic cancer indicators, the better and more reliable EuroCare's complementary indicators on cancer prevalence and cancer survival have become. The EU continues to fund projects and networks to update and harmonise data on cancer control in the Community. The EU Network for Information on Cancer (EUNICE), for example, continues some aspects of EuroCare and does important work in compiling, comparing, interpreting and disseminating information on cancer incidence and cancer care in Europe. It also carries out bench-marking and monitoring exercises. In addition, the Commission is working continually to encourage the coordination and communication of health data amongst Member States, as information is key to improvement in cancer control. One such initiative is the EU Health Portal, which will be launched later this year and will serve as a single access point to EU health-related information, with links to all Member States.



Among its many recommendations, the ASPECT report calls on the EC to urgently ratify the Framework Convention on Tobacco, and to give tobacco research its own funding line of 680 million euros

If the EC wants to benefit from consultation with well-informed and representative European Patient Groups, should it help with funding so those groups can avoid being reliant on sponsorship from the pharmaceutical industry?

MARKOS KYPRIANOU I believe that public health throughout Europe benefits from information being shared and pooled by as wide a range of stakeholders as possible, and the Commission works closely with NGOs to this end. The EU already funds many projects run by health organisations and European-level health networks, although there is much competition for limited resources. Ideally, European Patient Groups should not be overly reliant on sponsorship from any one source, however, whether this means industry or public funding.

Vince DeVita: the view from the top

➜ Interview by Chistine Haran

As director of the NCI between 1980 and 1988, Vince DeVita was a Commander in Chief of America's War on Cancer. He has little time for those who now criticise the plan of attack – or the outcome. But he warns that if we are to win the battles in the molecular arena, we will need to fight on an altogether grander scale.

Disillusionment with the speed of progress in finding a cure for cancer has led some people to question the vision of the 1971 National Cancer Act and the way it was interpreted as some sort of quasi-military campaign. Did you get it right?

VINCE DEVITA We had a very straightforward mandate to support basic research and the application of the results of the research to reduce the incidence and the morbidity and mortality from cancer.

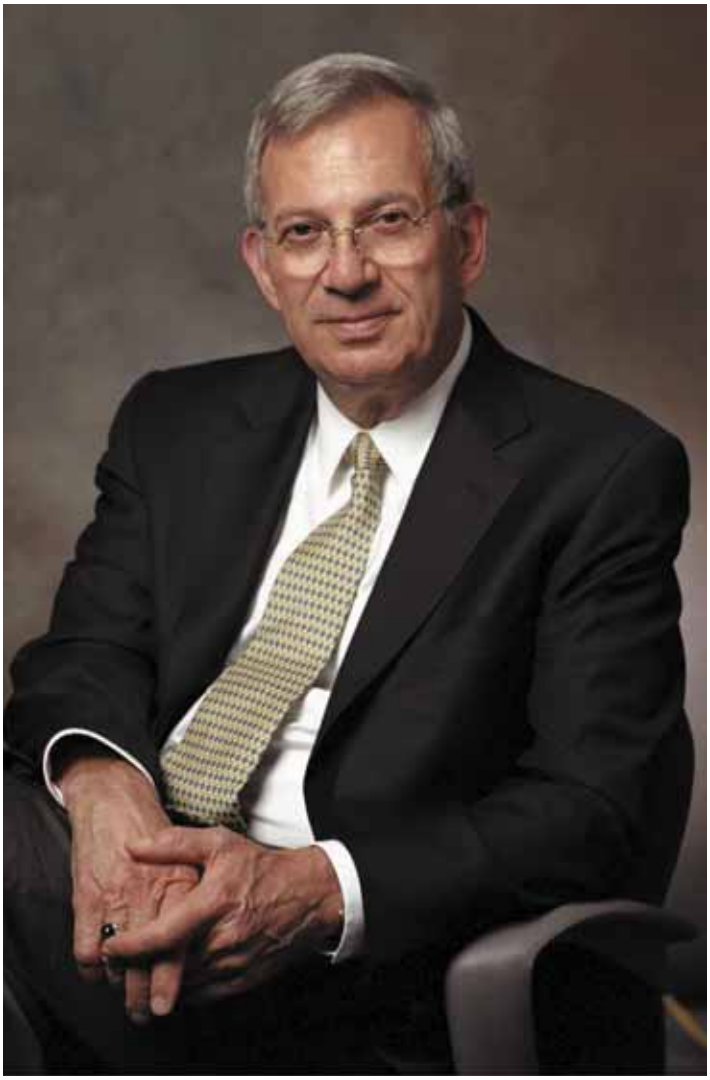
Period. End of story. What was so controversial about it? The National Institutes of Health [which include the National Cancer Institute] had never been involved in applications before. In fact they considered their job to be basic research, and the applications were done somewhere else.

That is why the Cancer Act was very controversial and everybody was against it, and if it wasn't for the fact that [advocate and philanthropist] Mary Lasker was so politically powerful it would never have passed.

Did the War on Cancer succeed?

VINCE DEVITA You hear and read that the War on Cancer failed, but actually it did everything it was supposed to do. It supported basic research handsomely. It has now spent about $50 billion on research, of which 80% has gone into basic research. It set up applications programmes – the EORTC [European Organisation for Research and Treatment of Cancer] and US clinical trials programmes. And what's happened to the incidence and morbidity and mortality of cancer? The incidence of cancer in this country started dropping in 1990 and has continued to drop every year since, and so has mortality. And the morbidity from cancer, comparing 1971 to 2005, is like night and day.

In 1971 when the Cancer Act was passed, a woman with breast cancer, for example, had a radical mastectomy and the breast was removed, all the muscle was removed and all you had was a thin layer of skin over ribs. Then women would get irradiated on top of that and their arms would swell up and neither the surgery nor the radiation did enough to cure the patient.



"I think the War on Cancer has been a resounding success, and I'm very pleased to have led it"

Nowadays you can have a lumpectomy and radiation therapy with a very good cosmetic effect, and you get adjuvant chemotherapy. Mortality has dropped in this country and survival has increased. Even though it's very difficult for a patient to be diagnosed with breast cancer and go through treatment, it's nowhere near as difficult as it was back then.

So every benchmark of the mandate has been hit and it's been hit in some places in Europe as well. I think the War on Cancer has been a resounding success, and I'm very pleased to have led it.

How did the NCI evolve under your leadership?

VINCE DEVITA When I became director in 1980, we created the cancer programme, as it was described in the Cancer Act. We reorganised the Institute so that it reflected treatment and prevention, and then we reorganised the treatment division. When I had taken over as director of the Division of Cancer Treatment in 1974, the treatment division didn't have all the treatment programmes in it. Drug development, for example, was in the treatment division, but supervision for all the clinical cooperative groups was in

"The whole ideal of the Cancer Act was to get these things going all over the world"

another division. So if you wanted to make the translation of a drug and put it in clinical trials, you had to go through another group of people. We put all the treatment programmes together where they belonged.
We also created the PDQ, the information system [for patients and health professionals]. We set up 11 bi-national agreements with European countries. We used the vehicle of cancer research to open up pathways to various countries, such as the Soviet Union. It was a frenzied time.

Was there any collaboration with Europe?
VINCE DEVITA In the beginning there was very little going on in Europe. So when the Cancer Act was passed there was a provision that Europeans could apply for grants through the National Cancer Institute. Thanks to people like Umberto Veronesi and Gianni Bonadonna in Italy and Henry Tagnon in Brussels, we had a receptive audience. So we set up the original grant for the EORTC. In Brussels, we also established a centre for drug screening, so our drug development programmes could access European cancer drug candidates. We provided money to the Istituto Nazionale Tumori in Italy for a biostatistical centre and for the CMF [cyclophosphamide, methotrexate, fluorouracil] clinical trials.
We did a lot in the beginning and the Europeans have done very well since. I think it's an important story because the whole ideal of the Cancer Act was just that: to get these things going all over the world, because what you learn in Europe is going to be applicable in the United States and vice versa.

What do you see as some of the more important recent contributions from European oncologists?
VINCE DEVITA The best work in Hodgkin's disease now is done in the German lymphoma study group. We have so many private doctors in this country who use yesterday's therapy that it's very hard to get them to put patients on tomorrow's protocols. The Germans do it. They put thousands of patients with Hodgkin's disease into a study, and all the major questions in Hodgkin's disease are going to be answered by the German study group. There have also been drugs of European origin; there's been good synergy in drug development.
But the Europeans still don't even come close to the US in terms of funding. The NIH budget is $26 bn a year. That probably exceeds the cancer research budget of the rest of the world. We're still the major defenders of the health of the world. They may not like me to say that but that's true.

How did you decide what research to fund in the early days of the War on Cancer?
VINCE DEVITA We did a lot of research contracts, which were very controversial. They were and are a dirty word in science. The reason people love grants is that if you're an investigator and you get an idea, you write a grant application and you submit it to the government. It's peer reviewed by scientists independent of you and you get a score. If the score is good enough, you get support. A research contract is somebody sitting at the NCI saying "I think we ought

"We're still the major defenders of the health of the world. They may not like me to say that but it's true"

At a hearing of the President's Cancer Panel, at the Columbia University Cancer Center. Though already director of the NCI, DeVita (second from right) is a relative youngster

"You need $20m mobilised from five institutions, with the research directed by a major scientist"

to look for viruses in cancer and we're going to put in $50 million," and we'll ask who wants to apply for it. The fact of the matter is we did a study, which we never published, looking at the major advances in science. We asked a small group of people to identify 15 areas where there had been major advances and then we looked at the funding. What we found out was that every instrument that we used to support research was represented: research contracts, grants, cooperative groups, and so forth. So it was fallacious to think that one mechanism could support research then and it's even more fallacious now.

What do you think about the way research is funded today?

VINCE DEVITA Science has moved from the era dominated by individual scientists to what we call 'goal-directed' research. With all of the tools we have available now, you can address almost any major question in the cancer field. We're exactly where we wanted to be. But this will require that we mobilise very large numbers of resources.

So instead of doing a project in an individual lab for $200,000, what you need is $20 million worth of resources mobilised from five different institutions, and have the research directed by someone who is a major scientist in that particular area.

The mechanisms for supporting the new kind of research just aren't there and need to be assembled on a project by project basis, which is very inefficient. So there really needs to be re-thinking of how we spend money to support research.

"The more specific a new targeted drug is against a target, the less effect it has against a cancer by itself"

Are clinical investigators getting the support they need?

VINCE DEVITA Again we're back to the investigator-initiated research grant. When somebody sits in their small laboratory and they've written an experiment and it's all done mostly with the equipment that's contained in that room, it's very easy to review that grant. When you look at someone like me, I wanted to treat Hodgkin's disease. I didn't have to apply for a grant because I was at the Cancer Institute, but my grant application would have said I want previously untreated patients from all 50 states. I'm going to have to have money to put them up in a hotel and I'm going to have to buy drugs. You put this in a grant application and they would say, "You've got to be crazy," and give it a low score and it would never get funded. Clinical research is logistically more difficult and has always been and continues to be under-supported.

What about translational research?

VINCE DEVITA The idea of translational research was to take something from a laboratory and translate it into the clinic. It's become a bit of a joke. There isn't anything anymore that isn't called translational research. Real translational research has been a problem and will always be a problem because a basic scientist has a PhD and he or she learns to focus like a laser beam on a particular problem, while an MD trains very broadly and then wants to be a clinical investigator and harness the basic and the clinical. But these two people usually don't understand each other. The people who are successful in developing things that apply to people are the ones who understand the systems and can bring them together. And that's where the administration of science is important. An administrator, like the director of the Cancer Institute, has to understand you have to do more than just talk about applying research. You have to set up systems that support the individual investigator who is making the translation from the lab. It's getting easier for people to see the applications of what they do, but we still have not reformed how we support research to take advantage of the shift in attitudes.

Where is cancer treatment headed?

VINCE DEVITA I think this business of goal-directed research has given us the opportunity to do things you could not do before, and I think there are huge opportunities and huge problems. For example, the more specific a new targeted drug is against a target, the less effect it has against a cancer by itself. Erbitux* is an example; if you use it by itself, it doesn't have that much of an effect, but if you use it in combination with another therapy, the effect is magnified. And I think you're going to find that with almost everything that's coming along.

Curing cancer is still going to require combination therapies, four drugs with four targets for example. So you have four great drugs, each one owned by a separate company, each one having very little effect on its own. The way you're going to cure cancer is to have all four together in a clinical trial. Yet it's very rare for a pharmaceutical company to join a clinical trial where each one puts their drug into a clinical trial. They want it to be approved by itself so they can get some return for their stockholder.

There needs to be somebody who, if they see these four companies that own these four drugs, is able to bring them together to have a clinical trial without hurting the financial interests of companies. In this country, you need to have a cancer director over all cancer programmes who is able to bring industry together with government, together with acadaemia.

What are your own goals for the future?

VINCE DEVITA I try to do a lot by pointing out where we need to go. That's what I think you should do when you get to be a senior statesman

ROBERT A. LISAK

In conversation with a colleague at the Yale School of Medicine, 1995

"You need a director over all cancer programmes to bring industry, government and acadaemia together"

in the field. I have an interesting perspective because I was in the unusual position at a very young age of sitting on top of the whole cancer world. It gave me the opportunity to think, see and do things differently than other people. I stepped down as director of the Cancer Center at Yale a year ago, but they gave me a chair and the freedom to do what I think is best to do in this area.

I'm on the boards of companies, such as ImClone, because you need companies. I've become the editor in chief of a new journal called *Nature Clinical Practice: Oncology*. And Samuel Hellman and Steven Rosenberg and I have our textbook, *Cancer: Principles and Practice of Oncology*, which just came out in the seventh edition.

We are very proud of this book because we've always tried to keep each edition of the book facing the future – books usually face backward. We think part of the reduction in mortality in this country is due to the textbook, because it put all of this information in one place where people could get a good handle on it.

I'm also writing a book on the War on Cancer with my daughter for laypeople. It's to explain to people what their $50 billion went toward and some of the difficulties that we faced. Explaining to people how difficult it was to get from there to here may make it easier for the money to be provided to get from here to there.

I have no intention of retiring. I've never stayed in one job for more than 10 years. You just change what you do.

* DeVita is a member of the board of ImClone, the company that makes Erbitux

Rising to the challenge in the developing world

Peter McIntyre

Most cancer deaths are in the developing world and the problem is set to escalate, yet cancer has never received the attention given diseases such as AIDS and malaria. Equipping less-developed health systems with the resources and expertise needed for effective cancer control has been posed as the great challenge of this century.

Cancer is seen as a disease of richer nations because it is strongly associated with aging, and the age profile of the richer nations is high and getting older. The perception has been that, while developing countries face huge problems from malaria, childhood diseases, waterborne diseases and AIDS, cancer is a problem for the future when rising affluence will also allow it to be tackled.

The reality is somewhat different. Last year more than six million people died from cancer globally – twice as many as died from AIDS. More than half of new cases were in the developing world and by 2020 it is predicted by the World Health Organization (WHO) that developing countries will account for 60% of 15 million new cancer cases each year.

Because of the rising incidence, unmatched by adequate measures to prevent, detect or treat the disease, deaths in developing countries overtook those in industrialised countries in the early 1980s. By 2020 there will be three cancer deaths in developing countries for every one in an industrialised country.

The result of this mismatch between perception and reality is that relatively little attention is paid to the millions of people who die each year in developing countries from cancer, without treatment, pain relief or dignity. Indeed, statistics about those who live and die with cancer are not even properly collected.

Indraneel Mittra, director general and head of oncology at the Bhopal Memorial Hospital and Research Centre in India, points out that although the prevalence of cancer may be lower in developing countries, the sheer numbers of people mean that the burden of cancer is high. "With the control of infectious diseases and increased longevity, cancer will become a more

Much of the data used in this article was presented at a Challenge Fund Meeting, *The Fight Against Cancer in the Developing World*, held in Rome, 20-21 January 2005, with the support of the Rome City Council and the European School of Oncology. Many of the quotations came from discussions or interviews at the same meeting. For more information about the Challenge Fund see www.cancerworld.com.

WHO / P. VIROT

A nurse recycles surgical gloves for the oral cancer clinic at the Tata Memorial Hospital in Mumbai (Bombay), India.

"Guidelines drawn up in the West encourage developing countries to focus on the wrong problems"

and more important problem." A number of traditionally very poor countries have experienced improvements in living standards and life expectancy, at least for segments of the population, and lifestyle changes can bring changes in the pattern of disease.

Tobacco's biggest market

Smoking has been gaining ground in the developing world for three decades. In China two thirds of men smoke. Smoking-related deaths in China are around one million a year today, and expected to rise to two million a year in 2025 and three million a year by 2050. In 1998 a study by Bo-Qi Liu, Richard Peto and others, based on interviews with relatives of some of the one million men who died between 1986 and 1988, estimated that half of today's smokers will die from smoking-related diseases, including cancer. The study predicted that tobacco will kill about 100 million males who were then aged 0–29 unless smoking patterns change. More than a third of these deaths will be from cancer – 15% from lung cancer, and between 5% and 8% each from cancers of the oesophagus, stomach and liver.

Other lifestyle changes have had an effect. Mittra says: "Breast cancer is increasing everywhere especially in the developing world. It is connected with the emancipation of women. She starts to work outside the home; she delays having her first baby, has fewer children and shortens the period of lactation."

Cancer is destined to become the leading cause of premature death in developing countries. The Global Alliance for Cancer Control, set up in 2003 by the International Union Against Cancer (UICC) and WHO, said: "Action is required now in order to save millions of lives in future years; cancer as a problem

TABLE 1. THE TOP FIVE CANCERS (BY INCIDENCE) IN THE INDUSTRIALISED WORLD, SOUTH ASIA AND UGANDA (MALE/FEMALE)

Industrialised countries	South Asia	Uganda (male)	Uganda (female)
Breast	Cervix	Kaposi's sarcoma	Cervix
Prostate	Mouth/pharynx	Prostate	Breast
Colon	Breast	Oesophagus	Kaposi's sarcoma
Lung	Oesophagus	Liver	Oesophagus
Lymphoma	Lung	Stomach	Ovary

Source for industrialised countries and South Asia, Audit in Oncology in the Third World, in: *Cancer in developing countries* S. Tanneberger, F. Cavalli, F. Pannuti. Source for Uganda figures, *Cancer Incidence in Five Continents VII* (IARC 1997).

cannot be put off for action by future generations. The time to act is now."

However, the pattern of cancer in developing countries differs from that in richer countries. Diego Serraino, an epidemiologist from the Italian National Institute for Infectious Diseases, says that this variation makes it all the more important to collect information about cancer incidence and cancer mortality. In Nordic countries population-based cancer registries cover almost 100% of the population. In Italy the figure is about 20%. In Africa, registries cover less than 5% of the population, and there are not even accurate data on cancer deaths. "Cancer registration in developing countries is a public health priority," he said.

The eighth edition of *Cancer in Five Continents*, published in 2002 by the International Agency for Research on Cancer, reflects this weakness. It contains data from north America and from 27 European countries, but only from 14 countries in central and south America, 12 in Asia and just 9 in Africa.

Variations in the incidence of cancer can be seen from Table 1, showing the top five cancers in industrialised countries, South Asia and Uganda.

In Asia and Africa there is a much higher incidence of cancers related to viral infections, notably hepatitis B (HBV), human papilloma virus (HPV) and AIDS, which is associated with Kaposi's sarcoma and non-Hodgkin's lymphomas.

Virus-associated cancers, particularly cervical cancer in women, liver cancer, Kaposi's sarcoma and non-Hodgkin's lymphomas, represent the predominant cancer epidemic in Africa. Indeed Serraino says that vaccination against HBV and HPV would constitute the most important primary prevention methods of tackling cancer in Africa. A prophylactic HBV vaccine is available today which could reduce the incidence of liver cancer. Therapeutic and prophylactic HPV vaccines are under development and could be commercially available in as little as two years. Even in the absence of an HPV vaccine, cervical cancer can be largely prevented through screening.

Combatting fatalism

In developing countries cancer tends not to be seen as a disease that, given the services and resources, can be detected and treated. Lack of awareness and lack of treatment options lead to late presentation.

In Nigeria there are fewer than 100 practising oncologists in a population of 120 million people, with limited supplies of drugs and imaging equipment. Muheez Durosinmi, from Obafemi Awolowo University teaching hospital, says that external aid organisations have failed to prioritise cancer, although Nigeria is expected to have 500,000 new cancer cases a year by 2010. "Cancer is for the most part an incurable disease in Nigeria, but less because of the nature of cancer, and more because of the limited resources and lack of education of the population."

Writing in the Newsletter of the International Network for Cancer Treatment and Research, Durosinmi reviewed the management of 213 patients with Burkitt's lymphoma and found that "similar to most other cancers" a large majority presented very late and were unable to afford anti-cancer drugs. More than

three quarters of patients presented with advanced disease, 62% received less than the recommended number of cycles of chemotherapy, almost 78% failed to return for their outpatient visits. Perhaps unsurprisingly there was a survival rate of only 1.9%.

Adedoyin Adesanya, a surgeon at Lagos University Teaching Hospital, recalls that his patients had to use clean, transparent plastic bags as colostomy bags until a nurse in Scotland arranged for supplies of left-over colostomy bags to be sent to him on a regular basis. Adesanya can offer sphincter sparing surgery, but the necessary equipment is usually unavailable and many patients cannot finance their operations.

ELIGIO PAONI

Adedoyin Adesanya: Cancer surgery in Nigeria is constrained by lack of resources

Of course the world is not only divided between rich and poor countries. Within many countries there is a contrast between services available to the poor and the rich.

Many Latin American countries are trying to expand coverage to the population that traditionally has not been able to afford care. Chile, Cuba, Uruguay and Brazil all offer 100% public care for those who cannot afford to pay, while Bolivia meets 40% of the cost of treatment. Brazil only has an equivalent of US$74 per person per year to spend on health care, but still manages to enrol patients into Phase 1 and Phase 2 studies.

Ten hospitals in Latin America, covering Argentina, Bolivia, Brazil, Mexico, Peru and Venezuela are collaborating in the Latin America Childhood Oncology Project, seeing between them 500 child cancer cases a year. One initiative is to establish a register of extra ocular retinoblastoma, the second most frequent extra cranial solid tumour in Latin America. Many children who present for treatment have stage IV cancers and very poor rates of survival.

Fernando Negro, from the CEHTAC Haematology Centre in Buenos Aires, says that with greater public awareness and greater equity in health care, they can make a real difference to outcomes of childhood cancers. "Are we winning? I believe the answer is yes. More than 70% of childhood oncology cases can be cured in developed countries, less in developing countries. 30% of the population is less than 15 years old in Latin America. But there are many inequalities in health care."

Pain relief

One improvement in care that could be made globally without huge cost is pain relief.

Cuba is a poor country with a well developed health care system. Cancer is the second leading cause of death and Cuba has been providing palliative care through community doctors and their teams since 1993. Today, 60% of people who die, do so at home, and health professionals are being sensitised to further reduce the number of people who die unnecessarily in hospital. However, community-based care is hampered by lack of morphine and weaker opioids such as codeine.

This is not just a problem for Cuba – 80% of the world's consumption of opioids is by 20 of the world's richest countries.

This is only partly a funding issue, as morphine can be made cheaply from a powder.

In Nigeria there are fewer than 100 practising oncologists in a population of 120 million people

It is primarily a result of restrictions on drug use in a community setting and bureaucratic problems.

Opioids are classified as narcotic drugs regulated by international treaties and national drug control policies. However the International Narcotics Control Board and the WHO both report that opioids are not sufficiently available for medical purposes. Reasons include a low priority for pain management, exaggerated fears of addiction and overly restrictive national drug control policies. A WHO Report "Achieving Balance in National Opioids Control Policy" (WHO 2000) proposes a set of 16 guidelines for countries.

These state: "National drug control policies should recognize that opioids are absolutely necessary for medical care, in particular for relief of pain and suffering" (guideline 2), and "Governments should establish and promote a national cancer control programme that includes cancer pain relief and palliative care as a priority for health care resources" (guideline 13).

Oncologist Stephan Tanneberger, based in Bologna, Italy, says: "We have to bring the problem of lack of morphine to the attention of the people who make the decisions. It is a limitation on the dignity of human life."

Building local services

Perhaps lack of attention for pain relief reflects a general sense of fatalism that prevents cancer from being given sufficient priority. The International Network for Cancer Treatment and Research (INCTR), an NGO founded by the UICC and the Institut Pasteur in Brussels, assists developing countries through collaboration in research, education and training. Its president, Ian Magrath, says that it is essential for countries to build the capacity of cancer services to break a vicious cycle in which governments give a low priority to cancer treatment and patients present with advanced disease and die without acceptable care.

Magrath believes that training doctors from developing countries in western institutions can be counter-productive. Many never return home while others are demoralised on their return by lack of resources. He also believes that guidelines produced in western institutions encourage developing countries to focus on the wrong problems.

"I am not against guidelines because everyone needs to know how to do things properly but you have to do clinical research in each country. We are using evidence from Europe and the USA to develop guidelines for these countries. We assume that the disease is the same, but the genetics and lifestyle are different. Guidelines must be based on the evidence and where is the evidence from developing countries?"

Franco Cavalli, President elect of the UICC, favours twinning programmes between countries, so long as they build local expertise and do not promote inappropriate hi-tech solutions. The aim should be to create conditions for independence, rather than dependency, and to encourage a "research minded attitude".

This year, for the first time, cancer control will be on the agenda of the World Health Assembly, the Governing body of the WHO, when it meets in Geneva in May 2005. An executive board resolution highlights the need to reduce the levels of smoking in developing countries, detect and cure cervical cancer and develop methods of multidisciplinary management.

It calls on countries to work with the WHO to develop cancer control programmes tailored to their socio-economic context, by considering four types of cancer:

- Cancers that can be prevented by avoiding exposure to risk factors
- Cancers amenable to early detection and treatment, including oral, cervical, breast and prostate cancers
- Cancers that can be cured or where a patient's life can be significantly prolonged, such as childhood leukaemia
- Advanced cancers where the programme should focus on relief from pain and other symptoms and to improve the quality of life

Perhaps the biggest task for the WHO is to convince policy makers that investing in cancer prevention, detection, treatment and care represents good value for money, given the other pressures on developing countries. The message from those in the front line is that that they can do a lot, if they are given the tools.

Does your hospital pass the palliative care test?

➜ Nathan Cherny and Raphael Catane

In a bid to raise standards in palliative care, ESMO has drawn up a list of criteria that hospitals must fulfill to qualify as centres of excellence. Would your hospital pass the test?

Everyone nowadays accepts that patients have a right to good palliative care, but too many treatment centres are still failing to deliver. Now the European Society for Medical Oncology (ESMO) has taken up the challenge to raise standards across the board, through an accreditation scheme that recognises and rewards centres that make the effort to get it right.

The ESMO palliative care working group has been working since 1999 to encourage medical oncologists and treatment centres to integrate all aspects of palliative care into their daily practice. They started off by publishing a set of standards for palliative care, considered the minimal acceptable for any cancer centre:

- Cancer patients receiving active therapy in cancer centres, and those with advanced cancer, in particular, should be routinely assessed regarding the presence and severity of physical and psychological symptoms and the adequacy of social supports.
- When inadequately controlled symptoms are identified, they must be evaluated and treated with the appropriate urgency (depending on the nature and severity of the problem).
- Skilled emergency care should be provided to patients with inadequately relieved physical and psychological symptoms.
- Patients with advanced cancer who no longer benefit from anti-tumour interventions should receive a continuous programme of palliative and supportive care.
- Social work and psychological support should be provided as part of routine care.

Now the palliative care group believe it is time medical oncology set its sights higher. Instead of focusing solely on minimal standards it is encouraging centres to aim for excellence, which includes a commitment to

ROLL OF HONOUR

Eight centres have so far achieved the status of ESMO designated centres in palliative care

- AZ Middelheim, Antwerp, Belgium
- Cork University Hospital, Wilton, Cork, Ireland
- Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland
- Klinik Dr. Hancken GmbH, Stade, Germany
- Kliniken Essen-Mitte, Essen, Germany
- Ospedale SS Giovanni e Paolo, Venice, Italy
- Ospedale Civile San Bortolo, Vicenza, Italy
- Velindre NHS Trust, Cardiff, UK

ESMO's palliative care working group aims to encourage oncologists to address their patients' physical and psychological symptoms and provide appropriate support as a routine part of patient care

Instead of focussing solely on minimal standards ESMO is encouraging centres to aim for excellence

educating staff in expert palliative care, participating in research, and ensuring that every aspect of support is effectively delivered to both the patient and their family.

The standards of excellence have been codified in 13 criteria (see p. 52). Centres that meet these criteria can apply for accreditation, which will bring them public recognition as ESMO designated centres for palliative care. They will also get special training grants to enable them to offer training to young medical oncologists looking to improve their skills in palliative care.

The applications are evaluated by the palliative care working group once a year. Successful applicants are announced at ESMO conferences and are listed in ESMO publications.

In 2004 ESMO received full applications from 20 centres. Eight were selected from six different countries (see box opposite). The unsuccessful applicants were encouraged to correct the deficiencies and reapply. Dirk Schrijvers, a medical oncologist with expertise in palliative care who sits on ESMO's working group said, "This is an ongoing quality improvement project and centres are encouraged to rise to the challenge, after which they receive the acknowledgement that they deserve. We hope that this programme will lead to improvement of cancer patient care throughout Europe by highlighting the importance of integrating palliative care in the routine management of all cancer patients."

Staff from the Ospedale SS Giovanni e Paolo in Venice – one of the eight hospitals accredited by ESMO for excellence in palliative care

Palliative care checklist

DOES YOUR HOSPITAL...

☐ **1. Provide closely integrated oncology and palliative care clinical services?**
Such centres demonstrate close integration between services with appropriate and routine cross-consultation. This includes: screening of cancer patients to identify patients with specific supportive and palliative care needs, availability of real-time supportive and palliative care interventions as part of routine cancer care, and availability of supportive and palliative care for all cancer patients receiving oncologic care.

☐ **2. Believe in continuity of care and not abandoning the patient?**
Such centres provide a continuity of care for patients with advanced cancer who can no longer benefit from anti-tumour interventions, with an ongoing programme of palliative and supportive care. This care may be provided on-site or in the community. In the case of physical care delivered by proxy by other services, the centre must demonstrate that ongoing support is maintained and that the centre provides backup services if and when needed.

☐ **3. Provide high-level home care with expert backup and coordinate home care with primary cancer clinicians?**
Expert home care services may be provided by the centre itself or they may be contracted out to another provider. In accordance with criterion 2, the centre must provide backup services and maintain coordination and communication regarding patients being cared for at home.

☐ **4. Support family members as a central part of the palliative care programme?**
Needs of the family members of patients with advanced cancer must be routinely evaluated. When required, the care team must provide psychological and social support to family members.

☐ **5. Provide routine patient assessment of physical and psychological symptoms and social support, backed up by an infrastructure that responds with appropriate interventions in a timely manner?**
The physical and psychological symptoms of patients with advanced cancer must be routinely evaluated. When inadequately controlled symptoms are identified, they are evaluated and treated with the appropriate urgency (depending on the nature and severity of the problem). Similarly, the social support of the patients is evaluated routinely and when inadequate support is identified, appropriate care interventions are undertaken. Specifically, if necessary, urgent respite care is provided. Inpatient palliative care is provided when home care support is inadequate.

☐ **6. Incorporate expert medical and nursing care in the evaluation and relief of pain and other physical symptoms?**
The evaluation and management of pain and other physical symptoms must be performed by the coordinated efforts of medical and nursing services in accordance with accepted professional standards.

☐ **7. Incorporate expert care in the evaluation and relief of psychological and existential distress?**
The centre must provide expert psycho-oncologic care. This may include care provided by psychiatrists, psychologists, chaplains, and any number of ancillary services, including music or art therapy, relaxation, and group therapy.

☐ **8. Provide emergency care for patients with inadequately relieved physical and psychological symptoms?**
Patients with severe physical or psychological symptoms that are not adequately controlled must be identified and receive emergency care either in the treatment centre or at home.

☐ **9. Provide facilities and expert care to stabilise symptoms in an inpatient setting?**
When necessary, the centre must admit patients with poorly controlled symptoms for supervised symptom stabilisation under expert care.

☐ **10. Provide respite care for ambulatory patients unable to cope at home or in cases of family fatigue?**

☐ **11. Provide facilities and expert care for inpatient end-of-life care and adequate relief of suffering for dying patients?**
Patients who are dying and who need inpatient care may be admitted to the centre for inpatient terminal care. Care must be provided by staff with expertise in end-of-life care for the patients and supportive care for the family. The adequacy of comfort of dying patients must be monitored and documented. End-of-life decision-making will be in accordance with the prevailing goals of care and respect norms of autonomy, beneficence, and local ethical norms.

☐ **12. Participate in basic or clinical research related to the quality of life of cancer patients?**

☐ **13. Provide education to help clinicians improve the integration of oncology and palliative care?**

Neoadjuvant studies offer mixed messages

Emma Mason

Three recent papers have failed to confirm any clear benefit of neoadjuvant treatment on overall survival. But its value in minimising the extent of surgery and its potential for greater survival effect using newer drugs may yet repay the faith many oncologists have in this approach to treatment.

Neoadjuvant therapy – the administering of any treatment such as chemo-, radio- or hormone therapy before the main local or locoregional treatment for a cancer – has an enthusiastic following amongst oncologists for several types of cancer. A growing body of literature points towards benefits in treatment, organ preservation and survival, but the benefits are not always clear-cut.

Survival

In a brief communication published last November (*JNCI* 2004; vol. 96, no. 22) Pier Luigi Zorat and his colleagues from the radiotherapy department, Ospedale Ca' Foncello, Treviso, Italy, reported results from a 10-year follow-up of a randomised phase III trial of neoadjuvant chemotherapy in head and neck cancer.

Their multicentre trial, started in 1986, enrolled 237 patients with non-metastatic stage III or IV head and neck squamous cell carcinoma (HNSCC). The patients were randomly assigned to receive either four cycles of neoadjuvant chemotherapy (cisplatin and 5-fluorouracil) followed by locoregional treatment (surgery and radiotherapy, or radiotherapy alone), or to receive locoregional treatment alone.

However, after 10 years it became clear that for patients with operable cancer, there was no statistically significant difference in overall survival between the two groups (22.7% for neoadjuvant treatment versus 14.2% for locoregional treatment alone). In contrast, there was a statistically significant survival difference for patients with inoperable cancer (16% versus 6%).

The authors conclude that: "Four cycles of neoadjuvant chemotherapy is a promising approach for treating patients with inoperable advanced head and neck cancer, but not for treating patients with operable disease."

Zorat and his co-authors say that neoadjuvant chemotherapy continues to be a common clinical practice for HNSCC in many centres, even though there is no evidence it does any good: "Current data do not support the use of neoadjuvant chemotherapy in HNSCC." They agree with the authors of previous studies, however, that it can play a positive role in minimising surgery to allow preservation of organs such as the voice box.

The authors accept that their study could be limited by the fact that, as it was started in 1986, there were older drugs in use and radiotherapy alone was the standard treatment for inoperable HNSCC. "Trials initiated after this study have demonstrated the superiority of concomitant chemotherapy and radiotherapy in locally advanced disease over radiotherapy alone."

They point out that research has yet to be done to establish the value of adding neoadjuvant chemotherapy before concomitant chemotherapy and radiotherapy for patients with inoperable HNSCC. "Our results provide a strong rationale for studies investigating this issue. The advent of new active drugs, such as taxanes, makes questions about the utility of neoadju-

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vant chemotherapy more interesting."
Zorat adds that it would be worthwhile limiting such studies with new drugs and new schedules to patients with inoperable HNSCC only.
"The benefits might be an increase in disease-free survival, while the disadvantages might be an increase in toxicity."
Jacques Bernier, director of the department of radio-oncology at the Oncology Institute of Southern Switzerland, Bellinzona, agrees. "The advent of 'new' drugs like taxanes – more recent, at least, than cisplatin and 5-fluorouracil – enables us to revisit the role of NACT [neoadjuvant cancer therapy] in head and neck oncology, both for unresectable disease and in patients to whom an organ preservation programme is applied. It is clear that we have now got more active drugs and that this observation paves the way for more investigation in the framework of NACT, and also with non-cytotoxic compounds such as anti-EGFR [epidermal growth factor receptor] and anti-VEGF [vascular endothelial growth factor]."
Bernier, who was the principal investigator of the European Organisation for Research and Treatment of Cancer (EORTC) study on the administration of concurrent cisplatin and radiotherapy in people with advanced head and neck cancer after surgery, believes that it is too early to be certain of the benefits of neoadjuvant therapy in head and neck cancers, even though it is being used more often now.
"It should not be considered a standard approach yet. For the time being, we have to test if NACT can be considered a safe approach in the framework of organ preservation programmes and can increase the disease-free survival and local control rates in unresectable disease. This needs confirmation."

Better local control

The results of a study of neoadjuvant treatment for rectal cancer, published last October, also failed to show any difference in overall survival. Rolf Sauer, from the department of radiation therapy, University of Erlangen, Germany, and colleagues compared preoperative versus postoperative chemoradiotherapy for patients with locally advanced rectal cancer (*NEJM* 2004; 351:1731-40).
Patients with clinical stage T3 or T4 or node-positive disease were enrolled in the trial between February 1995 and September 2002; 421 were randomly assigned to receive neoadjuvant chemoradiotherapy (radiotherapy and fluorouracil) and 402 to receive postoperative chemoradiotherapy (using the same doses as for the preoperative chemoradiotherapy

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with an additional boost of 540 cGy). The five-year survival rates were almost identical between the two groups – 76% and 74% respectively. However, there were other significant differences. The local recurrence rate in the neoadjuvant therapy group was just 6% – less than half that in the postoperative chemoradiotherapy group (13%). Grade 3 and 4 acute toxic effects occurred in 27% of the first group, compared with 40% of the second group, and rates of long-term toxic effects were 14% and 24% respectively. A statistically significant increase in sphincter preservation was achieved in patients from the neoadjuvant group whose tumours required abdominoperineal excision.

Neoadjuvant therapy also had an important effect on tumour stage. The authors report that "After preoperative chemoradiotherapy, there was a significant shift toward earlier TNM stages: 8% of the patients in this group had a complete response, according to histopathological examination of the tumour specimen, and only 25% (as compared with 40% in the postoperative treatment group) had positive lymph nodes (TNM stage III)."

But they also highlight the fallibility of tumour staging. "Eighteen percent of the patients in the postoperative treatment group had TNM stage I disease on histopathological examination of their resected specimen; all 18% had previously been found to have stage T3, T4 or node-positive disease on endorectal ultrasonography."

This could lead to early-stage tumours being over-treated in patients receiving neoadjuvant therapy, but the authors believe that innovative techniques such as three-dimensional endosonography and magnetic resonance imaging could improve the accuracy of staging.

They conclude: "Although no survival benefit was achieved with preoperative as compared with postoperative chemoradiotherapy, we suggest that preoperative chemoradiotherapy is the preferred treatment for patients with locally advanced rectal cancer, given that it is associated with a superior overall compliance rate, and improved rate of local control, reduced toxicity, and an increased rate of sphincter preservation in patients with low-lying tumours."

Commenting on the study, Lars Påhlman, of the department of surgery (colorectal unit) at Uppsala University Hospital, Sweden, says "The treatment of locally advanced rectal cancer has already changed to neoadjuvant chemoradiotherapy; this study makes an important contribution with regard to low local recurrence rates."

He believes that improved chemoradiotherapy has the potential to

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improve not only rates of distant recurrences, but also survival rates. "The local recurrence problem has been solved with good surgery after neoadjuvant radiotherapy. The next step is to concentrate on distant metastases. Therefore, I do believe that up-front chemotherapy for some months, followed by radiotherapy and finally surgery will be the next step."

Surgery remains key

The importance of surgery and of not relying exclusively on neoadjuvant therapy is underlined in a third paper, 'Neoadjuvant versus adjuvant systemic treatment in breast cancer, a meta-analysis' by Davide Mauri, Nicholas Pavlidis and John Ioannidis, which was published this February (*JNCI* 2005; vol. 97, no. 3).

They evaluated nine randomised studies of breast cancer patients treated either with neoadjuvant therapy (chemotherapy or hormone therapy) or with adjuvant therapy, between 1983 and 1999. The meta-analysis included 3,946 women, regardless of whether they had been treated with additional surgery or radiotherapy or both.

The results showed no difference in overall survival, disease progression or distant metastases between the neoadjuvant and adjuvant treatment arms.

However, neoadjuvant therapy was associated with a statistically significant 22% increased relative risk of locoregional recurrences, especially in trials where radiotherapy without surgery was more common in the neoadjuvant arms than in the adjuvant arms.

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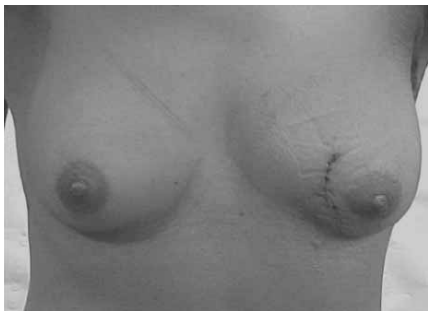

Neoadjuvant therapy can play a role in minimising surgery and thus preserving organs. In breast cancer, neoadjuvant chemotherapy can be used to shrink a tumour that would otherwise be too large for a lumpectomy. This will allow more women to save their breasts, though there will be a slightly increased risk for local recurrence

presence of an apparently good clinical response to neoadjuvant chemotherapy," say the authors. "Some sort of breast-conserving surgical intervention is likely to be warranted, regardless of whether neoadjuvant or adjuvant treatment is adopted and regardless of the patient's initial clinical response."

Monica Morrow, the G. Willing Pepper Professor of Cancer Research and chairperson of the department of surgical oncology at the Fox Chase Cancer Center, Philadelphia, USA, argues that the results of the meta-analysis do not mean that neoadjuvant therapy should be abandoned for breast cancer patients – just that surgery should always be included as well.

"Everyone needs surgery after neoadjuvant treatment. There is no reliable way to tell if all the cancer is dead, and in most cases it is not, so surgery facilitates local control."

The authors agree. Ioannidis, chairman of the department of hygiene and epidemiology at the University of Ioannina School of Medicine, Greece, says: "What the meta-analysis shows is that neoadjuvant treatment is not better than adjuvant treatment in terms of hard clinical outcomes; it is worse for local recurrences if surgery is not performed. This is not an issue when surgery is performed as well."

Morrow says another interesting finding from the study was that neoadjuvant therapy did not necessarily mean that more breast cancer patients were spared mastectomies and could have breast-conserving treatment (BCT) instead.

This was partly because many of them were already candidates for breast conservation. She says the increased risk of local recurrence in women receiving the neoadjuvant treatment might also be due to the fact that, although the therapy may shrink the tumour, it is still difficult for surgeons to be sure whether or not the tissue around the margins of the tumour is disease-free.

However, says Morrow: "BCT should not be avoided in women getting neoadjuvant treatment, but neoadjuvant treatment (outside of a trial) should be reserved for women who need it in order to be able to have a lumpectomy.

"Right now, some women get neoadjuvant therapy who could undergo an initial lumpectomy, because it seems like a good idea. This overview shows no hint of a survival benefit with this approach, but some downside with regard to the surgery. On the other hand, if the tumour is too big to do a lumpectomy without neoadjuvant treatment, the small increase in local recurrence is worth it because it will still result in more women saving their breasts."

Pavlidis, professor of medical oncology at the University of Ioannina School of Medicine, points out that all the studies in the meta-analysis used older, second-generation anticancer drugs, including mainly anthracycline-based chemotherapy, and that therefore it is not safe to extrapolate the results to newer drugs with different modes of action. "Further research and longer follow-up results from the ongoing studies using taxanes or trastuzumab [Herceptin] combinations are urgently needed," he says.

But would newer drugs produce any difference in survival between neoadjuvant and adjuvant therapy? Ioannidis says: "One might speculate that with more potent chemotherapeutical regimens, survival might improve, but this might be equally so either with neoadjuvant or with adjuvant chemotherapy; neoadjuvant use may not have necessarily an extra benefit."

Try it and see

As with the two previous studies mentioned here, the meta-analysis raises a number of further questions. For instance, could neoadjuvant therapy serve to identify early on how well patients respond to a particular treatment, so that if they respond well, a shorter course could be given, while a poor response could enable doctors to switch to a different therapy?

"Right now, patients are given a fixed number of cycles of neoadjuvant treatment whether or not they respond", says Morrow. "It would be interesting to do a study of switching to a different therapy after one or two cycles of treatment if there is no response, to see if that provides a better outcome. Markers that predict response are desperately needed, and will only be found from neoadjuvant trials," she said.

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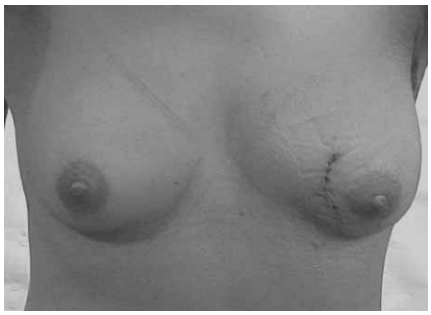

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Cancer vaccine for CML shows promise

Vaccines have long been seen as a potentially attractive option for treating cancer. Now a group targeting a peptide that plays a key role in CML think they may be onto a winner.

An Italian team of researchers has shown for the first time that a vaccine against a BCR-ABL-derived peptide can provoke a clinical response in patients with chronic myelogenous leukaemia (CML). Results from the 16-patient study of the vaccine, named CML-VAX100, were published in the *Lancet* (19 February 2005, p 657).

The target peptide, p120, is key to the pathology of CML as it is the product of the fusion gene, BCR-ABL, that forms with the characteristic Philadelphia chromosome mutation.

No company has directly expressed an interest in the vaccine to lead investigator Monica Bocchia of Siena University, whose team shares patent rights with US investigators. She said companies were welcome to talk to her about the possibility of developing the product, but the team was determined to go ahead with a Phase III trial even without commercial support, particularly as the vaccine is not difficult to manufacture. She would be approaching Italian co-operative groups about the study using CML-VAX100 plus imatinib versus imatinib alone.

Although Novartis's BCR-ABL tyrosine kinase inhibitor, Glivec (imatinib), has revolutionised CML treatment, there is still a lot of work going on to further refine therapy. Patients with chronic phase CML tend to have a rapid response to the treatment – they can achieve a complete cytogenetic response within six to 12 months – but molecular remissions are rare. "The eradication of residual disease (and possibly the cure) without bone marrow transplantation still seems a difficult goal for a tyrosine kinase inhibitor approach alone," note the study authors.

Very effective

In the *Lancet* study, CMLVAX100 was "very effective" in inducing a specific immune response say the authors – 70% of patients had a positive delayed-type hypersensitivity reaction and most generated a CD4 proliferative response. In an accompanying commentary (p 631), Saswati Chatterjee and K Wong of the City of Hope National Medical Center in California say it is "reassuring" that antigen-specific responses were generated in the trial.

Ten patients started the trial after 12 months of imatinib treatment, while six patients started after six months of treatment with interferon.

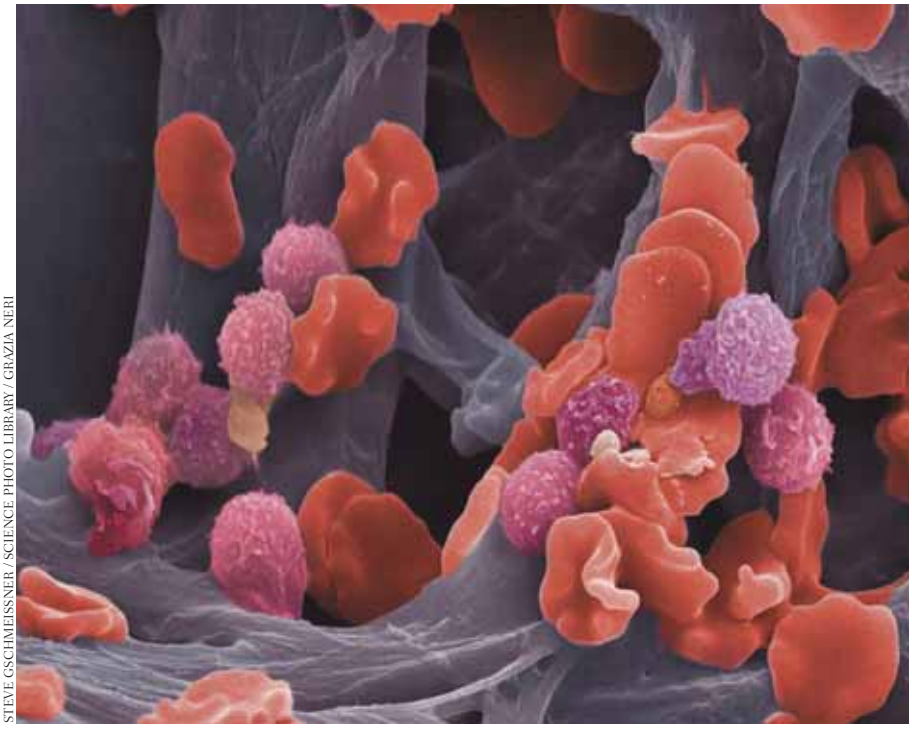
In the imatinib group, in which all patients had stable cytogenetic disease (median duration 10 months) at the start of the trial, apart from one with stable complete cytogenetic remission, all patients had improved cytogenetic responses after six vaccinations over 11 weeks. Five patients reached complete cytogenetic remission with three of these having undetectable levels of mRNA transcript from the BCR-ABL gene.

In the interferon group, in which patients had a median of 17 months stable residual disease before the study, all but one patient had improved cytogenetic responses and two reached complete cytogenetic remission. The degree of reduction in residual disease across the study seemed to correlate with the level of delayed-type hypersensitivity reaction.

All the patients received granulocyte-macrophage colony-stimulating factor (GM-CSF) and QS-21 as immune adjuvants. Wong and Chatterjee point out that, in previous studies, GM-CSF alone has increased the rate of cytogenetic remission in CML patients, but the dose was higher, so GM-CSF was unlikely to account for the success of Bocchia's trial.

Future option

CMLVAX100 is certainly a potential therapeutic option for CML in order to reduce residual disease and increase the number of patients who achieve a molecular response, the authors believe. Although the trial was not controlled, the speed of



STEVE GSCHMEISSNER / SCIENCE PHOTO LIBRARY / GRAZIA NERI

The proportion of patients reaching undetectable transcript levels contrasts with data on imatinib

response and the fact that three imatinib patients had undetectable transcripts make it likely that the vaccine had an effect on the patients in the study, said Bocchia.

The proportion of patients reaching undetectable transcript levels in a "very short period" contrasts with recent data on imatinib. A new molecular analysis of the IRIS study* showed that only 4% of patients in complete cytogenetic remission after imatinib treatment had undetectable transcripts, while this figure rose to 30% in patients with an early cytogenetic response.

Wong and Chatterjee say the development of vaccines against BCR-ABL or other CML-specific antigens appears to be a "reasonable avenue for further investigation" given the early promise of efficacy, ease of administration and lack of toxicity. However, they caution that there have been many disappointments in the history of work on tumour vaccines for CML, comparing the progress of development to the labours of Sisyphus.

The Phase II study with CML-VAX100 has now expanded to 22 patients. As well as plans to take the product into randomised Phase III trials, Bocchia's team is working on another vaccine. CMLVAX100 is suitable for the 60% of CML patients whose disease is characterised by the b3a2 break in the BCR gene; the new vaccine will tackle the remaining 40% of patients with b2a2 disease.

The emergence of imatinib resistance supports the development of new strategies to treat the disease, says the commentary. Novartis and rival Bristol-Myers Squibb have certainly realised this. Both are working on candidates for Glivec-resistant CML, and other companies are focusing on drugs to counter the problem in another of Glivec's indications, gastrointestinal stromal tumours. One company working to develop a commercial CML vaccine is Antigenics. It is studying a personalised cancer vaccine, AG-858, in Phase II studies.

First published in issue 3031 of *Scrip World Pharmaceutical News*, 23 February 2005.

**The IRIS study (International Randomized IFN vs ST1571) is the largest CML Phase III study ever conducted. It compared the effects of interferon vs imatinib (Glivec) in 1106 CML patients treated at 117 centres in 16 countries*

Cancer vaccine for CML shows promise

Vaccines have long been seen as a potentially attractive option for treating cancer. Now a group targeting a peptide that plays a key role in CML think they may be onto a winner.

An Italian team of researchers has shown for the first time that a vaccine against a BCR-ABL-derived peptide can provoke a clinical response in patients with chronic myelogenous leukaemia (CML). Results from the 16-patient study of the vaccine, named CML-VAX100, were published in the *Lancet* (19 February 2005, p 657).

The target peptide, p120, is key to the pathology of CML as it is the product of the fusion gene, BCR-ABL, that forms with the characteristic Philadelphia chromosome mutation.

No company has directly expressed an interest in the vaccine to lead investigator Monica Bocchia of Siena University, whose team shares patent rights with US investigators. She said companies were welcome to talk to her about the possibility of developing the product, but the team was determined to go ahead with a Phase III trial even without commercial support, particularly as the vaccine is not difficult to manufacture. She would be approaching Italian co-operative groups about the study using CML-VAX100 plus imatinib versus imatinib alone.

Although Novartis's BCR-ABL tyrosine kinase inhibitor, Glivec (imatinib), has revolutionised CML treatment, there is still a lot of work going on to further refine therapy. Patients with chronic phase CML tend to have a rapid response to the treatment – they can achieve a complete cytogenetic response within six to 12 months – but molecular remissions are rare. "The eradication of residual disease (and possibly the cure) without bone marrow transplantation still seems a difficult goal for a tyrosine kinase inhibitor approach alone," note the study authors.

Very effective

In the *Lancet* study, CMLVAX100 was "very effective" in inducing a specific immune response say the authors – 70% of patients had a positive delayed-type hypersensitivity reaction and most generated a CD4 proliferative response. In an accompanying commentary (p 631), Saswati Chatterjee and K Wong of the City of Hope National Medical Center in California say it is "reassuring" that antigen-specific responses were generated in the trial.

Ten patients started the trial after 12 months of imatinib treatment, while six patients started after six months of treatment with interferon.

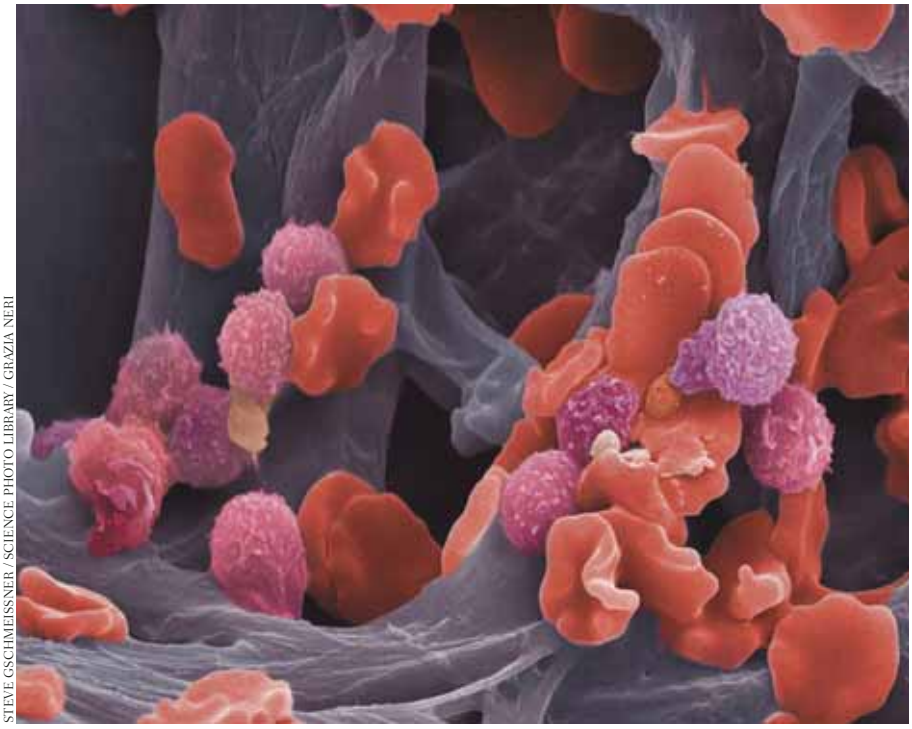
In the imatinib group, in which all patients had stable cytogenetic disease (median duration 10 months) at the start of the trial, apart from one with stable complete cytogenetic remission, all patients had improved cytogenetic responses after six vaccinations over 11 weeks. Five patients reached complete cytogenetic remission with three of these having undetectable levels of mRNA transcript from the BCR-ABL gene.

In the interferon group, in which patients had a median of 17 months stable residual disease before the study, all but one patient had improved cytogenetic responses and two reached complete cytogenetic remission. The degree of reduction in residual disease across the study seemed to correlate with the level of delayed-type hypersensitivity reaction.

All the patients received granulocyte-macrophage colony-stimulating factor (GM-CSF) and QS-21 as immune adjuvants. Wong and Chatterjee point out that, in previous studies, GM-CSF alone has increased the rate of cytogenetic remission in CML patients, but the dose was higher, so GM-CSF was unlikely to account for the success of Bocchia's trial.

Future option

CMLVAX100 is certainly a potential therapeutic option for CML in order to reduce residual disease and increase the number of patients who achieve a molecular response, the authors believe. Although the trial was not controlled, the speed of



STEVE GSCHMEISSNER / SCIENCE PHOTO LIBRARY / GRAZIA NERI

The proportion of patients reaching undetectable transcript levels contrasts with data on imatinib

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Symptom management at the touch of a button

Alex Mathieson

Side-effects of chemotherapy are nasty and can be dangerous. But soon patients may be able to log symptoms and receive prompt advice or, if necessary, medical attention, using nothing but a mobile phone... and a rather sophisticated computer programme.

An ambitious project based at the Cancer Care Research Centre, University of Stirling, Scotland, is setting out to help patients overcome the unwelcome effects of cancer chemotherapy through the use of mobile computer technology.

The idea is for patients undergoing chemotherapy to use hand-held computers and/or mobile phones to help them cope with their side-effects while at home. The technology gives patients information on self-management of certain reported symptoms and alerts medical staff to more serious problems that require immediate attention.

A research team led by Nora Kearney, professor of Cancer Care at Stirling University, recently completed a feasibility study which involved 18 patients using a hand-held computer. The team has also done early trials with mobile phones. The patients in the feasibility study, all of whom were undergoing chemotherapy, inputted data on their symptoms into the hand-held computer and sent it to a central server linked to their clinical centre. Here the data was automatically fed into an alert system devised to warn patients and staff of impending serious problems.

Early alert

"We want to be able to intervene early for someone who, for instance, is receiving chemotherapy for colorectal cancer and develops diarrhoea, which can be life-threatening," Kearney says. "Levels of alert have been built into the system based on what we know about the clinical symptoms from previous work. An 'amber' alert triggers a self-management protocol on the hand-held computer that will advise the patient on what steps to take, perhaps an antidiarrhoeal agent in the first instance. If three ambers are struck, a red alert is automatically triggered at the clinical centre with an immediate call-back to the patient from a nurse. Some defined symptoms, such as a high temperature, produce an immediate red alert."

The feasibility study builds on the work of the WISECARE initiative (Workflow Information Systems for European Nursing Care), which aimed to evaluate whether nursing care underpinned by practice guidelines and

Using this hand-held computer, patients can log their symptoms and send them to their treatment centre. Software at the centre will monitor the information, and grade it for levels of alert. At an amber alert, standard advice will be offered to the patient via their computer about steps they can take to relieve the symptoms. A red alert triggers an immediate call back from one of the nursing staff

information technology would improve patient outcomes. Patients in the WISECARE study (over 300 in number) listed their symptoms on a paper questionnaire that nurses then had to transfer to the electronic patient record when the patient visited the clinic, with interventions being based on the resultant scores. Kearney's project aims to cut out the paper-filling exercise and allow patients to enter data directly into the system. "Nurses involved in the WISECARE study told us that the process of data entry to the system was time-consuming, and patients said it would be better if they could get access to self-management information quicker," Kearney explains. "The new system addresses both problems and allows symptom assessment and management interventions to be completed in real time."

Patients were involved from the outset in designing the software and interface

Interventions in the feasibility study were based on protocols that members of the research team had built into the system following extensive reviews of the literature, analysis of patient data and testing with clinicians. Patients reported their symptoms using a modified version of the chemotherapy symptoms assessment scale (C-SAS), which asks whether the patient has the symptom, how bad it is, and how much it impacts on his or her functioning.

This generated a 'score' which corresponded with specified interventions within the protocol. General information about cancer and treatments was also available to patients through the technology.

Patients were offered a brief teaching session on the hand-held computers from one of Kearney's research team prior to entering the study. "Some of the patients, particularly older ones, worried that they would have problems, but none of them had difficulties. Indeed, most managed it with ease," Kearney says.

Keeping it simple

The key to making the system user-friendly was to keep it simple. Patients were involved from the outset in designing the software and interface, and this paid significant dividends. "We went into the clinics and worked with patients to find out what they wanted," Kearney explains. "They raised simple issues we might not have considered – like some patients thinking the instruction 'home' on the computer meant it should only be used in their own home. That made us think hard about the use of language and the value of graphics."

Kearney's experience of using hand-held computers in the feasibility study and mobile phones in other work is leading her to conclude that the latter might be the better option for the longer term. "Each has merits," she says. "The hand-held computer has a bigger screen and you can get lots of information on it, but mobile phones are easily available and people are more familiar with them."

While early results are encouraging, the challenges of devising and running a system such as this should not be underestimated, Kearney warns. Although the research team was determined that no patient would be excluded on grounds of age or diagnosis, the system will not be suitable for all patients, particularly those with severe cognitive or perceptual disabilities. And any project that involves technology is bound to raise suspicions about expense in the longer term.

In addition, the work involved in putting the protocols together is enormous. "Protocol building is complicated and has taken the best part of seven years to get to this stage," Kearney concedes. "A huge amount of work has been necessary in reviewing literature and analysing data received from WISECARE patients to identify their symptom profiles over time."

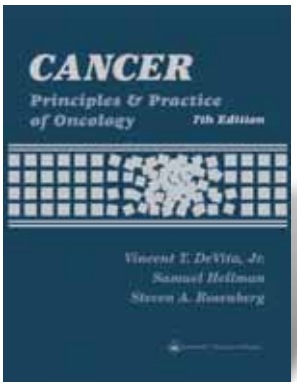
Scaling up

Kearney is nevertheless optimistic about future prospects. "The number of patients involved in the feasibility study was small, but they told us they felt their symptoms were managed better," she says. "Even though they weren't physically in the clinical area, they felt they could instantly send information about a problem to their clinicians."

Clinicians' initial scepticism also proved unfounded, Kearney claims. "When we interviewed clinicians post intervention, they told us they could see the benefits and that the system was enhancing their relationship with the patient, rather than replacing it," she says.

Kearney and her team are now putting together plans to launch a larger, multi-centre clinical trial in the UK to test the system's effectiveness.

Oncology
under the microscope



➜ Raphaël Brenner

This latest edition of *Cancer: Principles and Practice of Oncology* is a one-stop shop for everything you ever wanted to know about oncology.

As with shopping, so with books. If you are the sort of person who prefers to shop in department stores rather than at your corner grocery, this completely revised, updated edition of *Cancer: Principles and Practice of Oncology* is your kind of textbook. Consisting of 65 chapters and around 3000 pages, with 355 contributing experts, the book covers every possible aspect of oncology and aims to help practitioners "keep abreast of the latest scientific advances in oncology as they apply to clinical practice, as well as to provide a critical and practical guide to the optimal management of cancer patients."

The authors' commitment to the molecular biology approach is manifest throughout the book, particularly in the sections devoted to treatments (including biotherapeutics).

The book is divided into four sections. Parts One and Four, titled respectively Molecular Biology of Cancer and Newer Approaches in Cancer Treatment (gene therapy, preventive vaccines, etc.) forcefully demonstrate that diagnosis and the development of new treatments are based on an understanding of specific molecular targets.

Part Two, Principles of Oncology, deals with the principles that underline cancer prevention, diagnosis, and treatment and includes an excellent chapter on the design and analysis of clinical trials.

Part Three, which is by far the longest, offers practical information for state-of-the-art care for cancer patients. In addition to the chapters on cancer types, including liquid and childhood tumours, there are chapters on cancer prevention, oncological emergencies, supportive care and quality of life. Two features deserve to be highlighted: the very detailed and up-to-date descriptions of treatments and the multidisciplinary approach to oncology. The chapters dealing with major cancer organ sites are co-authored by surgeons, medical oncologists, and radiation therapists, in order to provide readers with "an integrated multimodality approach to cancer care."

Cancer: Principles & Practice of Oncology *7th edition*
Edited by Vincent T. DeVita, Samuel Hellman and Steven A. Rosenberg
Lippincott Williams & Wilkins, 2005,
2898 pp, $275

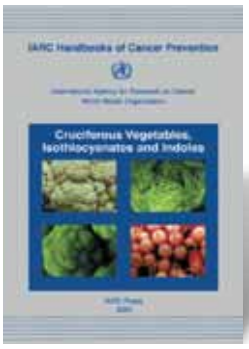
But while much space is accorded to the multidisciplinary approach regarding somatic aspects, psychological issues are minimally addressed. In this book, the disease, not the patient, is at the core of the physician's concern, which is a pity for a work that is considered a classic, and is indeed a highly comprehensive textbook on oncology. Since all the authors are North American, European readers may feel that the book reflects US points of view exclusively. This is especially true when it comes to certain therapeutic attitudes or in chapters devoted to specific US issues, such as the National Cancer Program or economic policies.

This said, the clarity of the texts and layout with its numerous illustrations and references are very helpful for oncologists and non-specialist physicians alike, aiming to deepen their knowledge on particular subjects. The book also comes with a CD-ROM containing the full text and illustrations plus a wonderful search engine.

Cruciferous Vegetables, Isothiocyanates and Indoles

IARC Handbooks of Cancer Prevention, Vol 9 - IARC Press, 2005, 213 pp $40

Cruciferous vegetables (cauliflower, cabbage, broccoli, wasabi, radish, etc.) account for between 5 and 25 % of vegetable consumption in Europe, and are important because they contain substantial amounts of glucosinolates (a group of compounds not found in other vegetables), which are hydrolysed to isothiocyanates and indoles. Experimental studies have shown that the latter compounds inhibit carcinogenesis through various mechanisms. However, as this book demonstrates in its thorough review of current knowledge related to the preventive effects of cruciferous vegetables on all types of cancers, the above results have only been partially corroborated by epidemiological studies. There is inadequate evidence to demonstrate that the consumption of cruciferous vegetables reduces the risk of cancer, except in the case of cancer of the stomach and lung, and even in these cancers the slight risk reduction is of the same magnitude as that for total vegetable intake. The authors thus conclude that cruciferous vegetables should not be promoted in preference to other vegetables in public education campaigns.



Internistische Onkologie

Edited by Wolfgang Wilmanns, Dieter Huhn and Klaus Wilms
Georg Thieme, 2005, 848 pp
euro 229

With its clear, structured approach, the editors of the 2nd edition of this textbook of internal oncology manage to cover all the main principles of oncology (histopathology, epidemiology, molecular biology), and deal with therapeutics and the main types of cancer. It describes in detail the indications and side effects of new cytotoxic agents, and the main chemotherapeutic protocols currently used in solid tumours.

The book is packed with instructive tips for dealing with oncology. It is written concisely, but not in an oversimplified manner, and the layout is as clear as the text itself, with many useful illustrations (particularly helpful in the case of the TNM classification), diagrams and tables.

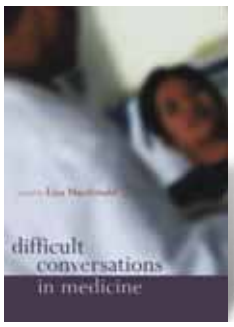
The book avoids presenting a boring catalogue of data, and instead reflects and illustrates the pluridisciplinary aspects of oncology. It also stresses the importance of evidence-based medicine.

The central importance of patients and their well-being are highlighted with an entire chapter devoted to supportive care, and to the psychosocial and ethical problems that arise in oncology.

Difficult Conversations in Medicine

Edited by Elisabeth Macdonald
Oxford University Press, 2005, 434 pp
£19.95

How do you tell a child that he or she has cancer? How should professional caregivers communicate with patients from different ethnic backgrounds? Although effective communication skills are essential in all aspects of clinical medicine, they are sorely lacking and all the more needed as a result of the development of technological medicine and the increased awareness and involvement of patients in their treatment. By depicting a wealth of cases and situations that confront physicians – dealing with cancer patients, with the elderly, or apologising to patients – this perceptive, original book offers much practical advice to physicians, including transcripts of conversations (with an angry cancer patient, with a patient who has a difference of opinion over treatment…), and proves that communication skills can be taught and learnt. As one of the authors writes, understanding the whole person and his or her concerns, and committing oneself to this relationship and this person is very demanding but also very rewarding. An insightful book, which will undoubtedly help health care professionals meet the needs of their patients.



Handbook of Cancer Chemotherapy
Edited by Roland T. Skeel
Lippincott, Williams & Wilkins, 2005
746 pp, $44.95

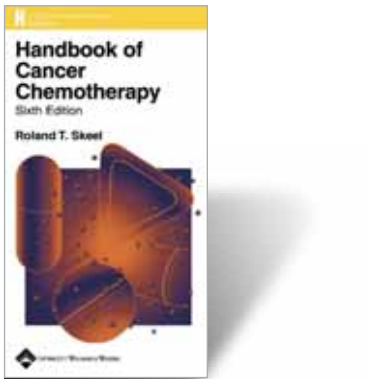
The Cancer Chemotherapy Handbook
David S. Fischer, M. Tish Knobf, Henry J. Durivage and Nancy J. Beaulieu
Mosby, 2005, 564 pp, £30.99

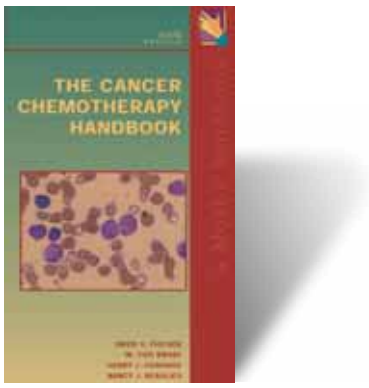
With the constant arrival of new drugs and biological agents on the market and the development of new combination regimens, the revised publication of these two classic handbooks is timely. Both books come in pocket size and follow the same model, listing first the chemotherapeutic agents and their use in alphabetical order, followed by the chemotherapies for adult human cancers according to type, and finally covering selected aspects of supportive care for cancer patients. The main difference is in the presentation of the therapeutic regimens.

Whereas Fischer & co. offer a brief introduction to each cancer type, followed by a compilation of the main common and less common chemotherapy protocols (in rough alphabetic order), quoting only the dosage, Skeel details, over 10–15 pages, the relevant clinical background data for each cancer type (epidemiology, diagnosis, staging…), before presenting, with many useful details, the various types of regimens for each condition. The latter book also provides a clear commentary on the rationale for choosing a particular therapeutic approach (prevention, surgery, radiotherapy).

These features make Skeel a particularly useful handbook for a wide range of readers – oncologists, medical students, as well as patients and their families who are looking for practical information about specific cancers and treatments. The compact, rather awesome layout is, however, a major drawback for the lay reader.

The Fischer handbook offers a more user-friendly, clearer presentation and an important chapter on the principles and applications of clinical trials (missing in Skeel), but it is obviously intended to serve a readership of oncology professionals.





Ces enfants qui vivent le cancer d'un parent
(How children experience the cancer of a parent)
Marie-France Delaigue-Cosset and Nicole Landry-Dattée
Vuibert, 2005, 140 pp, euro 16

"Health is incompatible with any form of denial," wrote the distinguished child psychiatrist Donald Winnicott. In the same vein, this important book, written by a physician and psychologist from the Gustave-Roussy Institute, reminds us that it is important to tell children the truth. Through many moving testimonies and in-depth analyses, the authors show how the untruths, secrets, and "deafening silence" of parents who are cancer victims cause immense suffering to their children, and how unresolved mourning can scar children for the rest of their lives. Cancer often causes patients to withdraw into their shells, but "when we are open and trusting towards others and unafraid of sharing painful truths, fears, and doubts, it is a sign that the disease has not destroyed who we are."

Disease, death and mourning, experienced in an atmosphere of truth and dialogue, do not harm children's development but, we learn, strengthen them and help them face difficulties in later life. Since children sense things much more sharply than adults, it is clear that lying can do more harm than good. Through Gustave-Roussy's support groups, many parents have been able to discover their children's strength and courage. "You are very strong, stronger than us," said one mother to her child. "I do not dare to say the truth, but from now on I will do so, because I know this is what you want."

Who pays the piper...

The advance of open-access publishing

The world's largest sponsor of medical research has brought open access one step closer by setting time limits for research it funds to be published online.

For around a decade, a group of campaigners has been arguing that the public should not have to pay to read the results of the scientific research which it has, through its taxes, financed. Feelings about the issue are particularly high when it comes to government-funded medical research. Patients' rights groups argue vociferously that it is ethically wrong to charge for access to the latest medical discoveries.

Needless to say, most existing publishers of such information, who make a good business out of selling it to what is more or less a captive academic audience, are not too keen on the idea of 'open access' – i.e. publication free to anyone. But open access seems to be on its way.

On February 3rd, America's National Institutes of Health (NIH), the world's biggest sponsor of medical research, announced that from May it will expect the research work which it has helped to finance to be made available online, to all comers, and free, within a year of that research having been published in a journal. The NIH also plans to make it easy for researchers to do its bidding by spending $2m–4m a year supporting an electronic archive into which these papers can be deposited. This will be managed by America's National Library of Medicine.

The NIH's decision represents a big change. The $30 billion that it spends on research each year leads to the publication of around 60,000 papers annually – some 11% of the total published in the medical field. Indeed, the organisation says that its actual impact is much higher, with 30–50% of the most important papers (the ones that get cited extensively by other researchers) having had NIH sponsorship. And although its new policy does not actually oblige its scientific dependants to make their work available this way, when a big paymaster asks its researchers to jump, in most cases the response is going to be "how high?"

A victory, then, for the open-access campaigners. But only a partial one. The NIH's announcement is actually a retreat from the proposal originally circulated last year, which was for open access within six months of first publication. The NIH appears to have backed down under pressure from commercial publishers, as well as from professional societies that fund their activities by publishing journals. Elias Zerhouni, the NIH's director, acknowledged that the step back was an attempt to "preserve the role" of these groups.

Nevertheless, in the publishing arena the NIH is something of a bull in a china shop. Even if it tries to tiptoe around, it is hard to see how there will not be some breakage. Dr Zerhouni himself touted the new policy as one that would "transform" and "change the landscape" of biomedical publishing. Publishers are going to have to find a way of adapting to those changes. The NIH is saying, in effect, that they could have as much as 12 months to make a profit. And while this may not please them, if any of the medical journals were to decide not to accept the new terms under which NIH

The NIH is saying, in effect, that they could have as much as 12 months to make a profit

COURTESY NIH

The US National Institutes of Health (NIH), Bethesda, Maryland

Patients groups argue that it is ethically wrong to charge for access to the latest medical discoveries

researchers must publish they would have to be prepared to lose a large proportion of their best research papers.

Another reason the NIH decision is important is that it could establish a standard for other organisations that fund research. The Wellcome Trust, a large charitable research foundation based in Britain, is also a strong supporter of open access. It is currently discussing with the National Library of Medicine the possibility of a joint, global archive of papers. Though by no means as powerful as the NIH, the Wellcome Trust helps to finance research that leads to the publication of around 3,600 papers a year. Ultimately the trust wants that research available free within six months of publication in a journal. For commercial scientific publishers the days of wine and roses may be numbered.