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John Smyth

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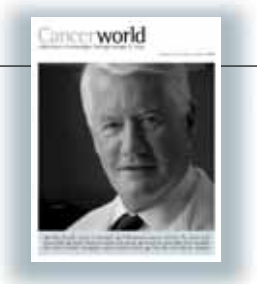

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A stronger voice within Europe

Kathy Redmond ■ EDITOR

An opportunity is opening up for Europe's cancer community to increase its influence over health and research policies, by overcoming its fragmentation to speak with a single voice.

The Federation of European Cancer Societies (FECS), the umbrella organisation for Europe's professional oncology bodies, is looking to transform itself into a single European cancer society vested with the authority to speak for Europe's cancer professionals as a whole.

Achieving this would be a huge step forward. But in today's Europe, it is the voice of the patient and of patient organisations that holds the greatest sway over politicians. Forming a strategic alliance between the people who use cancer services and those who provide and plan these services is therefore vital if Europe's cancer community is to maximise its impact.

The US cancer community provides many good examples of how such an alliance might work. The Cancer Leadership Council (CLC) is one. Set up in 1993 by eight cancer patient organisations with the aim of influencing health policy decisions, the CLC has expanded to include non-patient groups such as the American Society of Clinical Oncology (ASCO), the American Cancer Society, the Oncology Nursing Society (ONS), and the American Society for Therapeutic Radiology and Oncology (ASTRO). The CLC is now a 29-member forum, which takes positions on issues as diverse as stem cell research, reimbursement of clinical trials, regulation of pain medications and FDA guidelines. Policy makers listen because the views represent a broad spectrum of the US cancer community – not just physicians.

The American Federation of Clinical Oncologic Societies is another example. It is an informal coalition of professional oncology societies representing physicians, nurses, social workers and other health care providers, established to advocate for universal access to quality cancer care. Such informal alliances provide the opportunity for members to meet, explore issues, generate practical solutions, and develop plans for action without the hierarchy, costs and bureaucratic trappings of a formal organisation. Closer to home, the European Breast Cancer Conference provides a good example of a successful patient-professional partnership.

Whether the issue be inequities in access to quality care, bureaucratic clinical trial regulations or insufficient research funding, collaboration between patient and professional organisations can achieve far more than when each works in isolation. Given the recent establishment of a number of pan-European cancer patient advocacy organisations, and also the current focus on uniting Europe's professional cancer bodies, it is probably easier for this to happen today than ever before.

John Smyth: unity is strength

Marc Beishon

John Smyth likes to get things done. Head of a major research centre and member of EMEA's scientific advisory committee, he argues for closer cooperation between academia and industry. He also wants a stronger voice for oncology in Europe, and hopes to convince his FECS colleagues to opt for greater unity when he takes on the presidency this October.

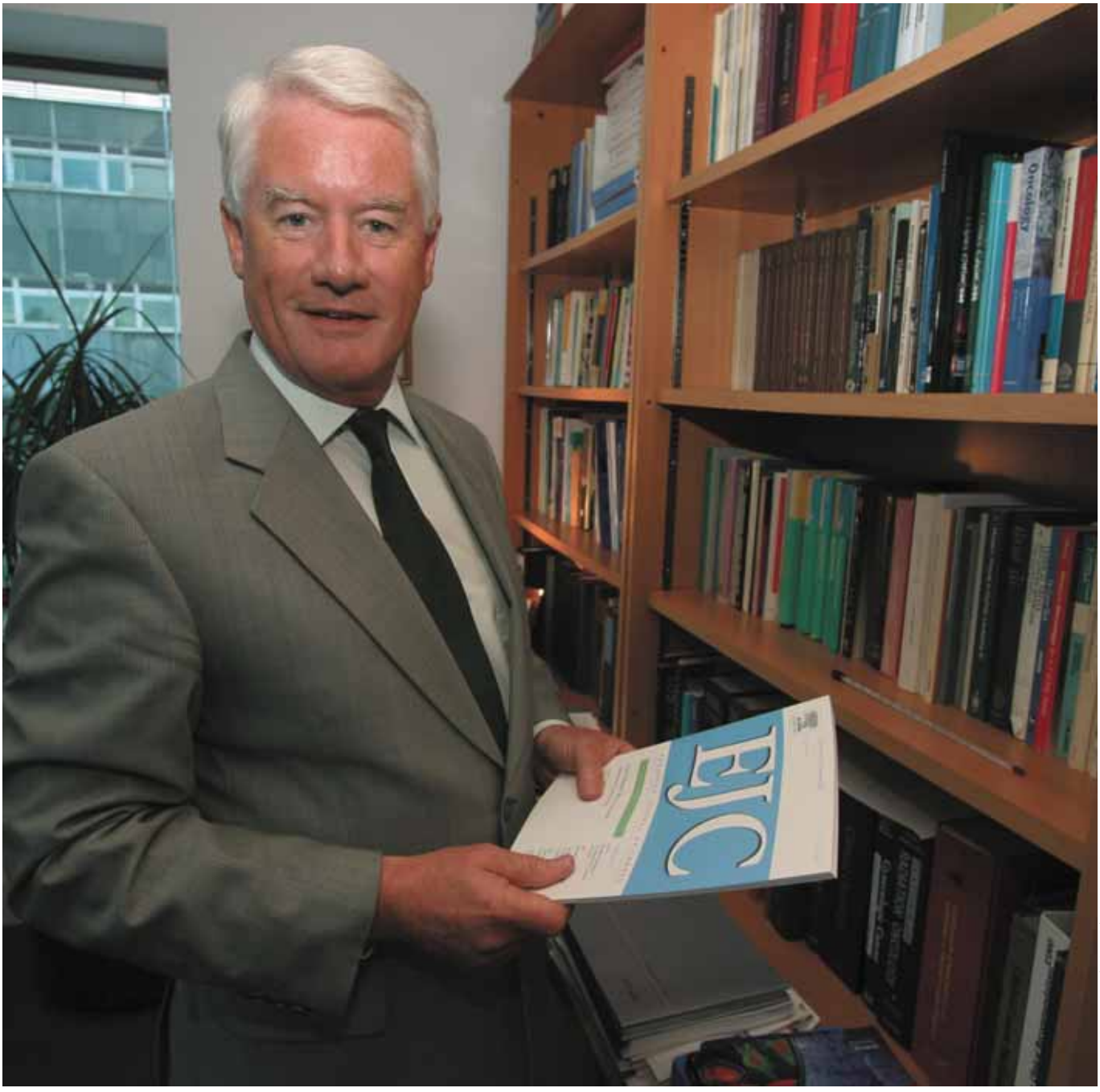
It's impossible to escape comparisons with the European Union when talking to John Smyth, the incoming president of the Federation of European Cancer Societies (FECS), and professor of medical oncology at the University of Edinburgh, Scotland. While the EU undergoes painful soul searching on its constitution, Smyth's mission for FECS is to bring about a fundamental switch to a single, unified organisation rather than a loose federation of societies. And of course one of the key aims of such unity is to work more effectively at EU level, to influence decision makers in critical areas of cancer research and treatment, such as drug licensing, clinical trials and care standards.

The unity theme extends further, as Smyth has been one of the early proponents of multidisciplinary oncology work that's been developing under his guidance since he took up his post in Edinburgh way back in 1979. He is now also the director of the Edinburgh University Centre for Cancer Research, which is housed in a new building alongside the oncology clinics at the huge Western General Hospital, and links with several other oncology-related units on site to form one of Europe's major cancer centres.

He's quick to emphasise that this multidisciplinary work does not mean bringing together just say medical and surgical oncology, but also psychology to help treat patients as a whole. In a field where the word 'holistic' is often bandied about, Smyth and his colleagues have a good claim for a strong, all-round patient management programme, which also includes a psychosocial research component.

"There aren't any trivial conversations in cancer, but I tell our trainees that it is possible to help everyone who comes through our door and that patients should feel comforted when they leave the consulting room. Knowing the medical facts is easy – any doctor can learn them – but getting communications right is hard. After all, one of the main reasons people go into medicine is to help others."

Good communications is also the key enabler for Smyth's work and ambition outside Edinburgh. He admits that there still is a lot of talking to do to persuade entrenched interests in



COLIN MCPHERSON / CORBIS / CONTRASTO

He stresses the importance of communications lines, particularly between industry and academia

"I'm concerned about the lack of mentoring and apprenticeship for young doctors"

the various cancer societies to share his vision for FECS – and he has of course witnessed at first hand the formation of divisions in the oncology community over the years, particularly in Britain.

Smyth's present commitments also include being the oncologist on the UK's Committee on Safety of Medicines, and he's on the scientific advisory committee at the European Medicines Agency (EMEA), where again he stresses the importance of opening up communications lines, particularly between industry and academia. "Most of my research has been on drug development, and the process of approving and licensing medicines is extremely important," he says, adding that there is too much at stake for 'snobbishness' about industry by academics to continue.

He has a platform to explore the academic issues – he is also the current editor-in-chief of the *European Journal of Cancer*, adding to a considerable workload. Apart from the administrative duties of running the cancer centre, and his international work, Smyth continues to see melanoma and ovarian cancer patients, teach undergraduates and direct research programmes (on ovarian cancer, melanoma and drug development). He's also a governor of the local hospice.

He does this with rigorous attention to time management and delegation, self-expressed "irrepressible enthusiasm and humour", and probably with the power of a beautifully modulated voice – Smyth was an international singer with the Monteverdi choir under the very demanding conductor John Eliot Gardiner, and he is possibly the only medical oncologist to have sung on stages from La Scala to the Lincoln Centre. Indeed, he went to the Cambridge University on a choral scholarship, but chose to read natural sciences. "I decided not to pursue music, largely because I had a brother who was a child prodigy on the piano and didn't want to compete with him." A second love was (and is) flying – he joined the Royal Air Force at Cambridge, and flies small planes today as a hobby. But thanks to a "general interest in science and people" he found himself studying medicine, moving to St Bartholomew's (Bart's) in London, and went on to benefit from a 'magical' training before the onset of more structured – and curtailed – development that doctors in Britain have to conform to today, according to Smyth.

"It's rare now in Britain for anyone to have the experience I did. As an oncology consultant, for example, I did some neuro, thoracic, paediatric, gynae and breast work. It's quite right now that you can't be an expert in all these, but I do think doctors have to specialise too soon these days."

As for medical oncology, Smyth was attracted to this then very new discipline by one of his mentors – and that's another aspect of his training that is 'disappearing' today, he feels. "I'm concerned about the lack of mentoring and apprenticeship for young doctors. I was fortunate in having two mentors who had a profound affect on me." The first was gastroenterologist Anthony Dawson (who became the Queen's physician) – "He had an extraordinary capacity to talk to people about chronic illness – I learnt a huge amount from him about talking to patients about cancer as a disabling disease.

"Both men helped me understand that you can face up to apparently appalling situations"

"Then I worked for Gordon Hamilton Fairley, really the founder of medical oncology in Britain. He had a fantastic capacity to talk to people about death. Both men helped me understand that you can face up to apparently appalling situations rather than do what a lot did then in the 1970s, which was not discuss such 'dark' matters."

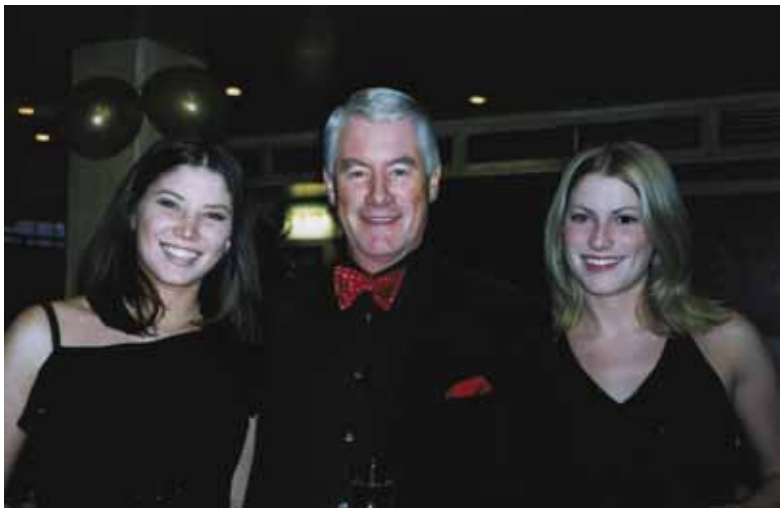
After working for Hamilton Fairley at Bart's he went to the Institute of Cancer Research at the Royal Marsden, where he did laboratory work and "had one of my few original ideas, about the importance of adenosine in lymphocyte metabolism, which resulted in pentostatin, a drug still used today to treat rare forms of leukaemia and lymphoma. This subsequently led to the widely used lymphoma drug, fludarabine."

This work got Smyth his PhD and a travelling fellowship to the National Cancer Institute in the US, where he "fell under the spell" of many more mentors, famous names in oncology such as Bob Young, Bruce Chabner and Vince DeVita.

He returned to the Royal Marsden, and then two years later was offered the professorship at Edinburgh, just after his 33rd birthday. "This was very scary, but I was able to draw on my cadre of mentors to help me. I was amazed to get the job – I didn't expect to have an academic career, as I was always middle-of-the-road in exams, but I was strongly inspired by the people around me in medical oncology."

Certainly the rigour of the US approach to drug development made a great impression – he says that those who feel the early chemotherapy days failed to deliver misunderstand medical oncology. "The Americans were very protocol driven and very good at publishing evidence, which you need to be when working with a narrow therapeutic index and sailing close to the wind between help and harm. They built up what we would now call an evidence base – and many Europeans went to the US to learn this discipline."

With hindsight, there was, he adds, a tendency to push on for too long with what worked for leukaemia and lymphoma, and to push therapies to the limit. "But I don't think anyone was seeking to cure cancer – there has also been confusion for the public who don't realise that cancer is a condition of the body, just like getting older."



With daughters Anna and Sarah at a family celebration

At Edinburgh, he found that surgical and radiation oncology were already well established, and added the third – medical oncology – component as part of a joint cancer centre effort. "This was partly out of necessity – I couldn't set up a centre in a big city on my own – but mainly because I believed in multidisciplinary working. It has served us well; we now have 21 consultants, all the clinics are multidisciplinary, and we have some 30,000 outpatient appointments a year."

Nor did he have to sell the importance of clinical research – there were already ongoing trials and he joined in by setting up a drug development and pharmacology lab, tapping into a high standard of medical expertise in the area that has long been a feature of Edinburgh. A training programme was set up, and Smyth's group established a good reputation for drug trials and relationships with industry, and became one of the leading British clinical research centres – in fact it was one of only two places earmarked for investment by the then Imperial Cancer Research Fund.

A standout development, and one that Smyth is especially proud of, was work with Glaxo on the first of the 5HT3 anti-emetic (anti-nausea and vomiting) drugs – his group conducted the first worldwide trials. "This has been one of the greatest contributions to patient tolerance of chemotherapy," he says. He was also a participant in the now defunct early clinical trials

Appropriate nerves before a live recording at the Salzburg Festival

group at the European Organisation for Research and Treatment of Cancer (EORTC), where he gained a lot of peer support and had fun meeting others – often at people's houses around Europe.

"While we were very conscious of physical toxicities we also wanted to learn about the emotional experience and what we now call quality of life," he continues, mentioning that his wife, Ann Cull, a research psychologist, set up a psychosocial oncology group and played a key role with the EORTC in establishing a group of quality of life researchers, with Edinburgh developing assessment tools. On-going work on what he terms "symptoms research" – not just sickness and pain but distress – has a current focus on fatigue ("a complex mix of the physical, emotional and psychological"), and ties in with Smyth's core interest in patient communications.

Where Smyth feels he has really taken a lead is with the clinical research effort, although it has been a struggle to reach the funding level the centre now enjoys, and also to attract staff. "It's much more challenging for scientists to work on human material. If you want a paper in *Nature* or *Cell* you work on clean, well-worked systems that will do what you want, such as yeast." Britain, he adds, is favouring basic research too much, while universities have become obsessed with research assessment and getting papers published in high-impact journals. "Clinical trials – including our first into man Phase Is – don't fall into this remit and the research is expensive. Clinicians get paid more than lab scientists, and universities don't have the resources to provide more lectureships and professorships."

An example: "We've just done some fascinating research on an anti-inflammatory medicine, with Fran Balkwill at Bart's, that may influence diseases such as ovarian cancer. But the value of such trials will only be realised in the lab, as we are looking at scientific end points." This drug – infliximab – is used, he says, to treat rheumatoid arthritis, but also inhibits the tumour necrosis factor. "So far it looks very encouraging in treatment of women with ovarian cancer. Applying science in such a dynamic clinical experiment has been very exciting."

As a centre, Edinburgh now looks to have considerable strengths. In addition to the regional clinical centre, Smyth's University Cancer Research Centre embraces research programmes on basic genetics and cell biology, a colon cancer genetics unit, research into prostate cancer and leukaemia and a combined programme investigating endocrine sensitivity and resistance in breast and ovarian cancer. Basic science and clinical research are linked by the drug development programme, which translates molecular and preclinical pharmacology to early clinical trials.

There are also ovarian and breast tumour banks, with many tissues having the advantage of full histories: "We not only know where the tissues came from but what happened to the patient subsequently," says Smyth. "We've been harvesting them for years. These tumour banks will be an absolute gold mine over the next ten

"These tumour banks will be an absolute gold mine over the next ten years or so"

"If FECS remains a 'talking shop' opportunities for a coherent voice in the outside world will be lost"

years or so." Another strength of Edinburgh, he adds, is simply having research people right alongside the hospital clinics. "As I travel the world I've found relatively few places where the lab and clinical complexes are physically joined up," he says.

Many of the successes and problems at Edinburgh will be familiar to those in other cancer centres, but as Smyth points out, one of the fundamental differences between Europe and the US is the former's wide diversity in patient and professional expectations and experience as you move among countries and regions. "The European oncology world has always been a complex mix, with great intellectual ability and good funding, but heterogeneity is the challenge – it's no good trying to impose say the British or French way on the rest of Europe."

FECS, he says, has been addressing issues such as clinical trials best practice and multidisciplinary working through workshops for junior oncologists. But there's a much bigger picture – the image and accessibility of the European oncology community as seen by healthcare decision makers, politicians, industry and the public. While FECS remains as essentially a 'talking shop' – albeit discussing important issues – opportunities to present a coherent voice to the outside world will be lost, says Smyth. As things stand, there are just too many interest groups competing for attention – and a single oncology society may have had a better chance, say, of staving off the worst of the European clinical trials directive, "which has been an absolute disaster for academic research."

"I realise that people are worried about loss of identity and visibility but I think that you can be an important part of a big enterprise as well as a small one." Certainly, FECS and other bodies such as the EORTC and the European Society of Medical Oncologists (ESMO) – of which Smyth is a past president – have made concerted efforts to lobby on issues such as the trials directive and the recognition of medical oncology. But Smyth is angling for the professionalism and clout that a unified society can bring, and comments that there has been too much "amateurish" lobbying work and protectionist behaviour.

A case in point in Britain, he says, stretches back to the 1980s. "With medical oncology still fairly new we formed the Association of Cancer Physicians – and the radiotherapy people were so jealous they set up the British Oncological Association. This year, for the first time, we are finally having a single meeting." If people are serious about multidisciplinary working, there should be no room for big egos and professional jealousies, he says. That names for disciplines around Europe are confusing and inconsistent – such as what comes under 'clinical oncology' – and that some professionals have private practice to protect, makes the situation yet more challenging, he adds.

"We are spending too much time and money duplicating efforts, with people massaging their egos in little fiefdoms," he says. "Ultimately, this is about improving patient care by providing greater equality of access to drugs and equipment around Europe. We stand a much better chance of doing this as a unified society than by arbitrary lobbying by small groups."

The situation is compounded too by the proliferation of meetings, which are "seriously out of control", according to Smyth. This is partly driven of course by the huge increase in industry money over recent years, but he feels professionals are now faced with an impossible choice of events. "I could be away 40 weeks of the year and not necessarily be any wiser," he says, adding that getting the right mix of new materials and the right people is often hit and miss. But he considers meetings and workshops to be pivotal to professional learning – "Education isn't about handing out recipes from a textbook or a journal. You

"Education isn't about handing out recipes from a textbook. You need debate and discussion"

need debate and discussion. Cancer medicine is a very difficult and subtle art form – you add science to the art. It's so easy to do something that is useless, harmful or just misleading."

Smyth would like to see fewer meetings, appropriately themed at certain times, and which also open up more balanced debate on the implications of research. Again, he hopes that FECS – or son of FECS – will be able to help streamline events.

He notes the standing ovation given to a Herceptin (trastuzumab) breast cancer trial paper at the last American Society of Clinical Oncology (ASCO) meeting, but is concerned that the ensuing headlines are picked up by patients and lobbyists without prior debate about cost implications and priority setting for treatment and screening. "Glivec is another good example – drugs like this can place huge unscheduled burdens on our health funders. But these 'irresistible' drugs don't come out of the blue – results are known well in advance of the big announcements and we should have systems that allow governments to anticipate research. We have to take responsibility for the hype and curtail it to allow data to settle in a more mature way."

Part of the streamlining process involves drug licensing and relationships with the drug industry. Smyth's primary interest in drug development, extensive consulting work and positions on the British and European approval bodies have given him considerable insight into pharma's workings – although some decisions remain a mystery. "We have to have a more open, honest and practical dialogue with industry. Over 25 years I've seen the attitude that academia is ethically pure and industry is commercially tainted. While such views may have had some validity, we have to recognise now that pharma has extraordinary financial resources, some of the world's best scientists and the best technology. My contact with companies tells me that unless the science is sound and the medicine works they will not try and sell it."

For EMEA, his hope is that it will offer an equivalent European licensing marketplace for the industry to the US Food and Drug Administration, where most commercial activity is currently focused. This should come about as recognition grows that Europe has different priorities to the US and may offer a better route to market for some drugs. Smyth adds that EMEA's scientific advisory committee is also very keen to open up dialogue with industry to make sure that 'pivotal' Phase III trials are done to a high standard, with the result that medicines are made available faster to the public. "It's tragic when millions of euros are spent on a Phase III trial that is poorly conceived and we can't give a licence – not because of the end result, but because the protocol was not well designed. I've had recent experience of this, and it is hard to understand why companies set out on expensive trials that are fatally flawed."

However, while it's in everyone's interest to shorten time to market, he adds that he's not happy with some recent fast-tracking – in particular Iressa (gefitinib), which was approved in the US from non-randomised trials, and which has higher toxicity than anticipated. "The pendulum

"With more treatment opportunities than we can afford, how do we prioritise?"

has swung too far away from our previous very conservative stance," he says.

While stressing that the oncology world needs to play its part in becoming much better organised, Smyth says that societies – nations, that is – have to create ways of involving the public in healthcare decision making. "It's one of the things I'm really interested in and it fits in with my remit at FECS and drug licensing – and I've spoken on public platforms about it. With so many more opportunities for cancer research and treatment than we can afford, how do we set priorities? It's absolutely clear to me that such decisions are not for doctors or lobbying groups alone, but in Britain I know of no public forum where we argue the case for healthcare."

While noting that the EU breast cancer resolution is a good example of effective lobbying, he comments: "You will always find people who support breast cancer for well understood reasons – but it's a pity if society has to fall back on groups of vulnerable patients and a few spokespeople who can argue their case."

Meanwhile, healthcare administrators such as hospital directors should not be placed in a position where they have to choose between different cancer treatments. That leaves the politicians – and Smyth has no truck with the "unspeakable nonsense" they spout at election times. Those who do take responsibility have his admiration – such as the Finnish health minister who addressed the last European Cancer Conference (ECCO) meeting. "She said that ultimately she makes the decisions and stands by them."

He would like to see such debate more closely linked with health promotion efforts, mentioning that Scotland has one of the world's best melanoma databases – and although incidence in men has trebled in the last 20 years, survival has improved thanks to an allied education programme that has seen people presenting earlier. Prevention is another area he wants to devote more time to, especially strategies that target young people.

If all this sounds like far too much work for any one person, Smyth says his university will be giving him time out to do the FECS work – he's seen too many colleagues overloading themselves to make the mistake of stretching himself too thinly. Home life is probably less frantic now that his four daughters have grown up and are safely pursuing non-medical careers, and there's a country cottage to retreat to. His bass voice is now a bit too 'old' to sing on the big stage, but flying is very much on the agenda – he and his wife have recently flown over Mt Blanc and watched whales off the South African coast in a small plane – as he says, you can't think of any other problems once at the controls.

En route for Mont Blanc in a plane older than himself!

At 60, his immediate work ambitions lie in two areas. At FECS, in whatever shape it becomes, he's intending to take a more "harmonious" message to European politicians and professional groups, recognising though that a lot of time-consuming "listening and talking" will need to be done. In Edinburgh, with all the physical and manpower resources in place for a modern cancer centre, the push is on for translational research to be rolled out into clinical medicine and he's in no doubt that many new treatments will be available. "Also, I hope I'll be around long enough to see a recreation of interest in academic medicine in Britain," he adds.

But what really makes him tick are "family, champagne and humour – humour especially is a very important part of life, no more so than to cancer patients, for whom it's a coping strategy."

No doubt a few bottles will be opened too if he gets everyone singing from the same European hymn sheet.

On the road to a single European cancer society

Anna Wagstaff

Members of the Federation of European Cancer Societies are debating how to present a united front to win a better deal for research and treatment. But how can disciplines with different priorities and agendas speak with one voice?

ECCO 13, that great meeting and mixing place for the cream of Europe's oncology researchers and clinical practitioners, gathers in Paris this October against a background of momentous changes in oncology and Europe.

Rapid advances in molecular biology are opening a new era of targeted treatments, requiring scientists in basic, translational and clinical research to work together in an unprecedented way. At the clinical level, there is an accelerating trend towards specialisation of treatment by organ. The process, although uneven, is associated with better outcomes, raising questions of whether patients should be treated only by practitioners and units accredited for the relevant organ. Meanwhile, the expansion of Europe is opening up opportunities to disseminate knowledge and best practice. Debates over how heavily Europe invests in research, how it organises its research effort, what support it gives to clinical and paediatric research all require the cancer community to make its voice heard.

But concerns that the voice of European oncology is weak and divided have prompted a heated debate over the need to reform – or replace – the Federation of European Cancer Societies (FECS), the body that organises the biennial ECCO conferences. This debate is expected to culminate in the announcement of the launch of a single European cancer society.

FECS has been the voice of oncologists in Europe for a quarter of a century. It is an umbrella organisation for the six main oncology disciplines: the European Society for Therapeutic Radiology and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Society for Medical Oncology (ESMO), the International Society of Paediatric Oncology, Europe (SIOPE), the European Oncology Nursing Society (EONS) and the European Association for Cancer Research (EACR).

But critics argue that FECS is fundamentally flawed. It is organised chiefly along disciplinary lines and does not represent thousands of clinicians who treat cancer patients but identify themselves as organ specialists rather than cancer specialists – gynaecologists, urologists, or gastrointenstinal surgeons for example. Being a federation, it is difficult to speak with the full weight and authority of Europe's oncologists, unless the six member societies have a common line. Furthermore, while each member society continues to hold separate congresses, showcasing their

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Harry Bartelink: We want everyone under one roof, with one front facing the outside world and much closer contact between disciplines

achievements and highlighting their own issues, Europe's oncologists will never have the public profile or lobbying power that ASCO (the American Society of Clinical Oncology) offers to colleagues in the US.

Even the critics agree that FECS was a wonderful creation, bringing together oncology disciplines at a time when the concept of multidisciplinary treatment was in its infancy. Luigi Cataliotti, president of the European Society of Surgical Oncology (ESSO) remembers his first ECCO conference, 20 years ago, as a unique forum. "It was a completely different way to approach cancer. The principal of an ECCO conference is to listen to speakers you would not normally hear; to listen to basic researchers, or as a surgeon go to a medical oncology symposium."

However, almost everyone, including Cataliotti, agrees that FECS must adjust to some new realities.

Harry Bartelink, outgoing president of FECS, has led calls for oncologists to work more closely with one another. He says that, despite FECS nominally bringing everyone together, and despite its emphasis on multidisciplinarity and on bringing basic research to the clinic, member societies have always worked on their own. "The only overlapping item was the ECCO conference. Now we want to bring them under one roof, with one organisation, and one front facing the outside world, and taking great care to create much closer contact between the disciplines, as well as incorporating the organ-oriented specialists."

Bartelink believes that the current fragmentation is fatally undermining the efforts of the cancer community to make its voice heard. One result, he claims, is that cancer is missing out on research money, despite its high level of scientific credibility. "Other areas are getting more attention. That is somewhere that we failed, and others were stronger in promoting their own area."

His big fear is that the era of targeted drugs, each with a higher price tag than the last, could lead to a US-style two-tier health system developing in Europe, where only people who can afford a higher insurance premium get access to the latest therapies. He is convinced that a united voice from European oncologists will be far more influential in persuading governments and health insurance systems to provide the funding needed to ensure equal access to quality treatment, than if the task is simply left to medical oncologists. He also believes that a united oncology voice could play a role in persuading the industry to charge affordable prices.

Lex Eggermont, president of the European Organisation for Research and Treatment of Cancer (an affiliate of FECS), is another champion of the proposed European cancer society. For the last year he has been gearing up EORTC, which conducts most of Europe's clinical trials, for the new era of molecular biology and targeted treatments. The strategy is to make sure that, wherever possible, clinical trials comparing one outcome against another include a translational research element, using techniques such as gene profiling or genomic or proteomic analysis to distinguish which patients will benefit from which treatments.

Everything depends on getting basic/translational and clinical researchers to work closely – and to get the research funds. The EORTC is assembling a network of core academic institutes and cancer centres that are able to collect and store tissue, and have the labs and scientists to carry out high-tech analysis. It is building its own academic research fund with a view to providing seed money for what could be costly trials, and is hoping to convince the EU that its work is worth funding. It is advising research teams how to cope with the obstacles posed by the way the clinical trials directive has been implemented in each Member State, and is putting pressure on the EU to revise the directive.

Eggermont believes there are huge prizes to be won from exploring targeted treatments, so long as the cancer community can convince the public and politicians. He points out that EORTC receives funding from the US National Cancer Institute, while the EU refuses to contribute, a situation he describes as madness. "You need a unified organisation that is so powerful that the politicians could not avoid seriously dealing with it. I would argue for an organisation that would bring together the science and the clinical parts of the oncology world, represented on a board that will define policy, and prioritise programmes, education and training. By

bringing these all together within one organisation you would have a real powerhouse."

This sounds like the task FECS set itself three years ago, which included aiming to "promote the field of oncology by fostering a favourable environment in Europe for research, treatment and care, with the ultimate goal of providing optimal access to the best possible treatment for all European cancer patients."

But Eggermont believes that FECS failed to achieve its potential impact, largely because of its structure. "It is difficult for a federation to have a unified voice," he says, "because you have a conglomerate of independent bodies that are – I would not use the word 'obsessed' – but focused on their own world." He wants everyone to agree on priorities for a common, science-driven agenda.

These arguments have been around a long time, but at the end of last year they came to a head when the medical oncologists warned that if radical changes were not made, they would pull out and go it alone. This was no empty threat, because it is the medical oncologists – the ones who sign prescriptions and carry out clinical trials – who attract lucrative pharmaceutical industry interest in the ECCO conferences, and FECS and some of its member societies rely on this money to a greater or lesser extent, to finance their work. Consequently, much of this year has been taken up with discussions to find a way forward that everyone can live with.

This is not just a case of medical oncologists holding a gun to the head of other FECS societies. The need for change is recognised well beyond the ranks of ESMO. Eggermont, for example, is a surgeon, while Bartelink is a radiation oncologist. Moreover, there are many medical oncologists in the ESMO leadership, including its president Paris Kosmidis, who are deeply committed to the multidisciplinary approach and very reluctant to break ranks with other FECS societies.

At issue here is not *whether* European oncologists need to change the way they are organised, so much as *how*. In particular, how to achieve a more powerful unified voice for oncology as a whole, while ensuring that all parts of the European professional oncology world are effectively represented and able to address their particular challenges. How to strike this balance within the structure of a unified cancer society is the subject of heated debate between FECS members, who must each defend their own specialities, while benefiting oncology and the treatment of cancer patients as a whole.

ESMO

WHAT'S DRIVING ESMO?

Paris Kosmidis: A single, powerful European cancer society is essential so that Europe's top oncologists can win better recognition nearer to home

Europe's medical oncologists crave recognition. They look at the ASCO conference – that glittering US stage where medical oncologists parade in front of the world's media – and they want it. And with some reason. Despite a seven-fold gap in research funding, 50% of presentations at ASCO come from Europe, including a good proportion of papers presented at the prestigious plenary sessions.

The contrast could hardly be greater with Europe, where medical oncology is not universally recognised as a specialist discipline. ESMO president, Paris Kosmidis, says that this damages patient care, more than it wounds his members' pride.

"If you go to the US, in which medical oncology is the leading force for oncology, and you look at five-year survival and the treatment outcomes of cancer patients, it is much better than in Europe. They have well-organised training programmes, they have officially qualified physicians, and each cancer patient receives the proper and right treatment."

By contrast, in Germany, patients are routinely prescribed chemotherapy by gynaecologists whose primary training is in surgery, or by physicians who lack specialist oncology training. In other European countries, drugs may be prescribed by 'clinical oncologists' who are also responsible for delivering radiotherapy.

ESMO has been campaigning for years for medical oncology to be recognised as a specialist discipline. The society is conducting Europe-wide research into medical oncology services to establish, country by country, how many medical oncologists there are, how they were trained, the number of comprehensive cancer centres, which drugs are available and whether all cancers are treated properly.

ESMO has also built a network within EU countries working towards

greater homogeneity of training, with a minimum of five years. Where such training doesn't exist, ESMO tries to fill the gap. Currently ESMO is focusing on training programmes in Central and Eastern European countries, including Estonia, Latvia, Poland and Romania. "The progress they have made is really amazing," says Kosmidis. "We see these people coming to our conference and presenting their own research work." Medical oncology societies have been springing up fast in these countries, and are now busy disseminating the latest knowledge and lobbying their own politicians.

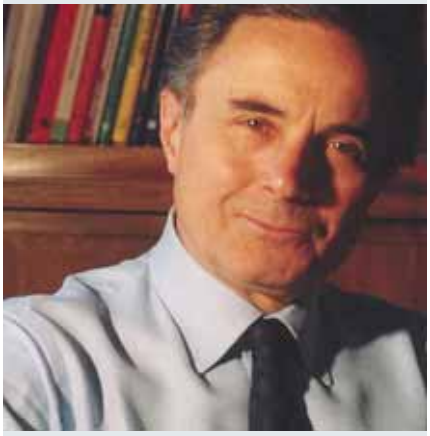
However, it is slow progress, and many European medical oncologists feel they are being held back by the lack of a public platform equivalent to ASCO. They hope the proposed single European cancer society may be able to offer such a platform. If not, the demands to go it alone will continue.

Kosmidis looks to ASCO as his model for the new unified society. This is a controversial choice, because although it is a society of 'clinical oncologists', it is dominated by medical oncology to the virtual exclusion of all else. Kosmidis argues this is justified by research and clinical reality. "If you compare the progress that has been made in surgery, radiotherapy and medical oncology, the difference is tremendous. The progress that has been made in the survival, quality of life and disease free survival is related absolutely and directly to the treatment of chemotherapy. If you look at colon, breast and lung cancer, you will see that all the most recent prolongation of life has come through targeted treatments. One example is Herceptin [trastuzumab], which will probably soon be given on an adjuvant basis. These patients live longer and certainly some of them will be cured. We've never seen that before."

Kosmidis would like to see the proposed European cancer society open to all disciplines, but based on individual members. "Members give power to the society. We feel that one society which is really multidisciplinary is an absolute necessity for Europe to make progress in treatment, prevention, palliation, education and in more powerful lobbying of politicians. It is our obligation as leaders."

ESSO

THE SURGEONS' CASE FOR UNITY



Luigi Cataliotti: A single society could provide space for multidisciplinary organ-specialist groups like EUSOMA, which cancer surgeons could relate to

Kosmidis will look in vain for other FECS societies to share his enthusiasm for the ASCO model. However, he can count on many in the surgeons' society, ESSO, to support a single, membership-based society, albeit from a different perspective.

The president of ESSO, Luigi Cataliotti, points out that surgery remains the single most important curative treatment for cancer, and becomes ever more central with early diagnosis. He wants an organisation that can attract all the surgeons who operate on cancer in Europe, many of whom do not see themselves as 'cancer surgeons'. Most of these surgeons do not work exclusively with cancer and identify themselves primarily as general surgeons, gynaecologists, urologists, head and neck surgeons, and so on. It has been difficult for ESSO to recruit them. While the Italian Society of Surgeons alone has a membership of 6000 – a large proportion of whom do cancer operations – ESSO's entire European membership languishes at around 2,000 surgeons.

Paradoxically, Cataliotti believes a single cancer society could be the answer, because by breaking down the boundaries between disciplines it would provide a space for multidisciplinary organ-specialist groups that cancer surgeons could more readily relate to. This would also tackle what he sees as the main professional issue facing ESSO – persuading surgeons to become part of a truly multidisciplinary culture.

"The first thing that a surgeon has to lose is the principle of being a 'prima donna'," says Cataliotti. "A 'prima donna' surgeon is not a good

"The first thing that a surgeon has to lose is the principle of being a prima donna"

Between 60% and 80% of drugs given to child cancer patients are not licensed for use in children

surgeon treating cancer, because you have to accept the collaboration of others. When we visit a patient with breast cancer, we start together, the radiologist, the pathologist, the surgeon, the plastic surgeon, the radiotherapist and the medical oncologist, from the beginning – not after the surgical treatment. Patients have to follow a very well-defined pathway. This is the main issue, to create this mentality."

ESSO has discussed turning itself into a federation to which organ based societies could affiliate, but the latest proposals for a single European cancer society are now seen as a possible way forward, although enthusiasm within ESSO for dissolving into a larger society is by no means universal.

Cataliotti is also currently President of EUSOMA, the European Society of Mastology, which has blazed a trail with guidelines on training and accreditation of all the disciplines involved in treating breast cancer, and accreditation of specialist breast cancer units. He is convinced that organising around multidisciplinary organ-based groups is the way to go, and talks of fledgling groups already in existence for urologists, coloproctologists, lung surgeons and others.

"Very often small hospitals exist in Europe where patients with a gastric cancer, for example, are treated by a surgeon who at the same time operates breast, colorectal, and thyroid cancer. Governments have to be convinced that to improve cancer outcomes, they have to accredit units, accredit specialists, and insist on proper training." He believes that a strong unified European cancer society would be ideally placed to convince them.

Cataliotti can foresee ESSO as a 'faculty' within a new cancer society, while EUSOMA will probably be the organ group for breast cancer multidisciplinary treatment. But he doesn't underestimate the problems in making such far reaching changes. "We can imagine what will happen in 5 or 10 years, but the first period will be difficult. We have a reality that has to be respected. ESSO exists, and the members of ESSO don't want to lose their identity. They want to recognise themselves. At the same time, EUSOMA members want to preserve the identity of a society of specialists who work under the umbrella of breast cancer, because it has been terribly efficient and constructive. The new society has to guarantee that surgeons or breast specialists can work together as a faculty or as a group."

The key question is whether cancer surgeons who did not join ESSO can be persuaded to join a unified European cancer society. "What ESSO members are saying is: 'Please take it slowly. Not in a few months, but in a few years, or we will lose the chance to encourage surgeons in all specialities with an interest in cancer to be members of the new society and to give their contribution to the multidisciplinary approach to cancer treatment."

SIOP EUROPE

PAEDIATRICIANS IN SEARCH OF A VOICE

Günter Henze: The voice of cancer in Europe must be strong; a paediatric faculty would provide adequate representation for the paediatric oncologists

The other group most inclined to value unity over autonomy is the paediatric oncology society, SIOPE. Paediatric oncologists have never had a problem with their own identity, but they feel appallingly let down by the political establishment and are looking for a powerful voice that can compel governments and the EU to pay more attention to children with cancer in Europe.

Between 60% and 80% of drugs given to child cancer patients are not actually licensed for use in children. The potential for lifelong damage by these powerful drugs and by radiotherapy is all the greater in bodies that are still developing. Paediatricians are desperate to see

targeted drugs developed for their patients, and for molecular markers that can tell them which children need intensive treatment, and which can be spared.

SIOPE president Günter Henze says that paediatricians do what they can with limited resources. They have a strong culture of international networking, reflected in the fact that the majority of child cancer patients (as high as 95% in Germany) are enrolled in treatment optimisation trials. He argues that this research-driven approach to treatment has caused mortality rates to fall faster in childhood cancers than in other cancers in recent decades. "We analyse the results, we look for strengths and weaknesses, and then adapt the subsequent trials to the results."

Because childhood cancers are too rare to be of much interest to the pharmaceutical industry, and in the absence of significant government funding, child cancer research is heavily dependent on charity funding – and vast quantities of unpaid overtime. But this fragile research base has been badly damaged by the EU clinical trials directive, which has made trials more bureaucratic and has more than doubled the cost of conducting a trial.

The paediatric system of research based treatment is not just underfunded, but is actually penalised in some countries. In Germany, health insurance companies have, on occasion, refused to pay for patients treated within clinical trials because they say it is science and not health care. Now the EU clinical trial directive is increasing the costs, particularly of international trials. Henze believes that this added burden is unsustainable, and says if the EU makes laws, it must also provide the financial support to make it possible to comply with them.

With the support of FECS, SIOPE has convinced MEPs to sponsor amendments to the Draft Regulation on Medicinal Products for Paediatric Use to guarantee that the needs of the academic sector are taken into account. Most of these were accepted at the first reading of the draft legislation in early September. However, the main focus of the Regulation is on encouraging pharmaceutical companies to undertake clinical trials for paediatric indications, by extending their patents for six months.

Henze says, "Trial protocols – highly complicated treatment plans – are being written by paediatric oncologists in the evenings and on weekends and holidays. This is serious work, and it has to be paid for. We cannot have a situation where pharmaceutical companies say 'we need this price' and the manufacturers of equipment say 'we need this price', and there is no money left for physicians and nurses. We are treating life-threatening malignant disease, and everything that has to do with these diseases cannot be an issue of charity."

Unlike the other FECS societies, SIOPE is not an independent society, but part of the international SIOP network. With no full-time secretariat of its own, and a pressing need for a greater voice at the political level, the prospect of being part of a powerful unified European cancer society is attractive, provided paediatric oncologists can trust that society to fight for them. Henze clearly believes they can. "The voice of cancer in Europe must be strong, and if we have a paediatric faculty within the society, I think this would give a reasonable representation for paediatric oncology."

ESTRO

RADIOTHERAPISTS ARGUE FOR A HALF-WAY HOUSE

Michael Brada: A cooperative of societies that could join forces where appropriate would be best. If everyone merges into a single structure, individuals may feel lost

Of all the FECS member societies, radiation therapists and oncologists are probably most happy with the status quo. There are no issues about recognition, as radiotherapists work almost exclusively with cancer, in tightly organised multidisciplinary teams concentrated in the larger hospitals and cancer centres. They are also relatively confident in their powers of political lobbying. Their priority, according to ESTRO president Michael Brada, is to ensure equity of access to high standards of radiation everywhere in Europe and promote research into improving treatment results.

Radiotherapy, he says, is given to 50% of all cancer patients and is the second most important curative treatment after surgery. It is also the most technical of the three clinical oncology disciplines.

A good service requires up-to-date equipment, adequate mechanisms to ensure that the equipment

works as it should, and investment to update radiation oncologists, physicists, biologists and technologists in the latest techniques and multidisciplinary approaches.

ESTRO recently completed a study of the radiation oncology needs in each country together with a survey of the availability of equipment and skilled personnel. The findings, says Brada, document huge discrepancies across Europe, and should provide a potent lobbying tool. "We want to make this information available for each individual country so that the societies within each of these countries can appeal to their governments that this is the standard that is required."

ESTRO has also put into place EQUAL, a Europe-wide quality assurance programme. Radiotherapy currently involves complex techniques, some of which allow far higher radiation doses than were previously possible, making the accuracy of dose delivered particularly critical. EQUAL developed quality assurance tools, and has a centre in Paris that provides quality assurance tests throughout Europe. At the same time ESTRO is encouraging radiation oncologists to lobby for quality assurance programmes within their own countries.

Education is also a priority, with 13 annual ESTRO courses as well as conferences. Brada says: "We feel that this education should spread to all European countries and everybody should have access to it, regardless of the wealth of the country." Attendances from Eastern and Central European countries in particular have been strongly encouraged through heavy subsidies.

ESTRO can point to notable lobbying success at EU and national levels, resulting in significant investment programmes in the UK and the Netherlands, improvements that Brada hopes will be replicated in other European countries.

ESTRO has also done better than other FECS societies in getting its hands on EU research grants, to finance – amongst other research – their work on quality assurance and the research into disparities across Europe.

Brada accepts that FECS needs to find ways to appeal to a broader layer of cancer professionals, and he is not hostile to the idea of a single European cancer society. But he would prefer a "cooperative" of societies rather than an individual member society. "I'm not sure our members want to be part of some enormous organisation where their voice gets lost.

"It would be much simpler if each organisation remains autonomous, but joins forces in activities that are better carried out together, such as PR, lobbying, annual conferences and educational activities. Beyond that, each one should be able to do what they need for their own professionals.

"If a single very big structure is created, individuals disappear and the leadership is just some distant headquarters. It is likely that everybody will get disenchanted and create a repeat of their own society."

EACR

Whose research is it anyway?

Bill Gullick: Even if the societies do merge, it won't be enough to make governments sit up and listen. It is the views of patient organisations that politicians care about

IF anyone has cause to be disenchanted, it is probably basic cancer researchers. EACR President Bill Gullick maintains an impeccable diplomatic silence, but he is clearly not happy with the direction of the debate. It could be that, as past president of FECS, he values the Federation and sees no need for change. But he and his members may also wonder what basic researchers will get from an organisation that cynics may claim has been created to satisfy the medical oncologists' desire to capture the limelight.

The targeted treatments that medical oncologists want to parade at a European equivalent of the ASCO conference are, after all, the result of decades of work by basic scientists,

Availability of radiotherapy equipment and skilled personnel varies enormously across Europe

"It is an exciting time for basic cancer researchers – the science is progressing at a dizzying speed"

delving into the way our bodies regulate themselves: identifying signalling networks, documenting genomic profiles, visualising and describing the genes, proteins and other components in molecular detail. Furthermore, the contribution of basic and translational researchers will be essential to the introduction and evaluation of any individualised cancer drugs in the future.

Gullick says: "This is a challenge for all of us. It involves a number of groupings who have not worked very closely before – basic scientists, translational researchers, biotech companies and pharmaceutical companies – as well as organisations such as the patient advocacy groups who can affect political decisions as to whether these types of medicines are made available."

Gullick's own laboratories at the University of Kent, UK, are currently investigating why only 30% of breast cancer patients who test Her+ respond to trastuzumab (Herceptin). Finding an answer to this question may prove vital in persuading governments to make this drug available as an adjuvant.

They are also trying to develop simpler tests that do not require DNA sequencing, and can be done in a standard hospital pathology lab.

Gullick sees resources for research as the biggest challenge. Like many others, he was shocked by the findings of a survey that showed Europe spends one-seventh of the amount invested in cancer research in the US. "Most of the problems of translational research are due to funding.

"There are three countries in Europe that invest around 400 million euro each – the UK, France and Germany. Then there is a group of countries such as the Netherlands, Sweden and Italy that invest around 50 million euro, and the rest have effectively no spend on cancer research at all. So one of the issues is: why is there such an enormous heterogeneity of activity?"

Despite lack of investment and poor career opportunities, which cause many young scientists to opt for other professions, this is a stimulating time for basic cancer researchers.

The science is progressing at a dizzying speed and scientists are enjoying the experience of working close to the clinical frontline and seeing the impact they are having on patients.

Gullick is excited by the younger generation who do opt for cancer research. "We've just chosen the EACR Young Cancer Researcher Award, and to say I was impressed is an understatement. We had five or six candidates who were simply outstanding. We are going to sponsor them to go to ECCO to present their work to give an opportunity for other scientists to hear these results and learn from them."

He is equally excited by the potential of young scientists from Eastern and Central European countries. EACR has been making considerable efforts to draw them in, particularly through its fellowship programme, which offers a chance to work in some of Europe's leading cancer research institutes.

One result is that the EACR conference has been rapidly growing in both size and stature – Gullick is particularly pleased to be welcoming leading medical oncologists like José Baselga to the next EACR conference.

More than 700 people attended last year, among them an American researcher who said that if a conference of such a high scientific level had taken place in the US, it would have had an attendance of 7,000. That shows, says Gullick, that the problem is not with the quality of Europe's scientists.

Given the pressing need to convince the politicians to put more money into cancer research, the prospect of a single, powerful cancer society might seem attractive. But Gullick believes governments only listen to patient organisations, and think that scientists are interested in science for its own sake. "We are seen as a special interest group and treated as any other special interest group."

A unified cancer society could deprive researchers of the public profile they are beginning to build, after decades of pioneering work. If the new society bears any resemblance to ASCO, they have every reason to fear the spotlight will fall on clinical researchers, eclipsing the contribution of basic research and their need for resources.

EONS

Nurses on the sidelines

Jan Foubert: I think we will get more by working with European nursing organisations, but if there is a new European cancer society, we will keep the door open

Oncology nurses are equally sceptical about a new unified cancer society, although for different reasons. EONS president Jan Foubert argues that FECS never acted as a truly multidisciplinary society and that the proposed new structure is likely to be even more narrowly focused.

The Federation, he says, never lobbied for the nurses' cause, though Foubert accepts part of the blame, saying that EONS should perhaps have demanded more. But he says that while EONS did participate in meetings, they never felt their voice was heard. He cites as one example the lack of response by the other societies to EONS' suggestions for adding a nursing research element to proposed clinical studies.

"When they talk about multidisciplinary, they mean the surgeon, the radiotherapist and the oncologist. For me, and for most nurses, it also means nurses, psychologists, dieticians, physicians – all the people who are taking care of the cancer patient."

Well-trained cancer nurses, he argues, are absolutely essential to providing adequate patient care. They spend more time with patients. They support them and their families, advising on nutrition and ways to cope with stress, nausea and fatigue. They play a key role in symptom management, advising patients about treatments to alleviate pain, anaemia or neutropenia, and teaching them to recognise when symptoms need immediate attention. In short, good oncology nurses are vital for addressing the problems that cancer patients find hardest to live with.

The trouble is, only a few countries offer nurses the training or responsibility to fulfil this role, and there are wide discrepancies across Europe. In some countries becoming a cancer nurse requires a full extra year of training; others require only a one-day course, or modules. EONS is campaigning for oncology nursing to be fully recognised as an accredited speciality throughout Europe, but fundamental differences in cultural approaches to nursing make this an uphill struggle. While some countries see it as an academic profession, with degree and PhD courses, others regard nursing as strictly vocational. In some countries, you can become a nurse at 16 years of age.

The focus of EONS has therefore been on education. They have put together a core oncology nursing curriculum, which details contents, contact hours and how the courses should be taught. However, it is not a recognised European standard, and each country chooses its own approach.

A new EU initiative, the Bologna Agreement, is set to change all this, through a common European model for higher education. Under its terms a nursing qualification will be defined as a bachelor's degree, and further bachelor standard qualifications will be required for specialist nursing. This offers a uniform system where nurses need a degree and a further degree in oncology nursing. EONS is restructuring its core curriculum to fit the competency-based Bologna model, and wants its course to be the starting point for discussions on an oncology nursing curriculum.

EONS has also constructed courses on such topics as fatigue management, nutrition, and most recently on haematological toxicities (TITAN). The take up of courses is increasing as oncology nurses become more organised and as EONS gains experience in administering courses for different nursing cultures in many languages.

In eight years, the number of national societies in EONS has risen from 22 to 28, with Bulgaria the latest of an influx of countries from Eastern and Central Europe. The fact that 23 societies expressed an interest in the TITAN course illustrates the impact that EONS is having.

EONS has gained respect and self-confidence and now seems to have escaped from the shadow of the medical disciplines in FECS. "We have become an independent organisation, with our own strategy, business plan and sponsoring, our own good conference and our own partnerships with industry," says Foubert. It has also found itself a new strategic umbrella group, in the recently formed European Federation of Nurses (EFN), a body with EU status that has as its aim to "strengthen the status and practice of the profession of nursing and the interests of nurses in the EU and Europe". EONS is part of the European Specialist Nursing Organisations section of the EFN and has a seat on the EFN General Assembly.

Foubert says bluntly, "I think we would have more chance to have oncology nursing recognised as a specialty by working with European nursing organisations than by working with the current FECS." However, he is advising the EONS council to keep the door open to any new European cancer society: "We should participate in the months and years ahead to see how this new society will look. You have to keep talking and hope these people will listen to you."

Did somene say unity?

Six FECS societies reflect six different sets of problems, and conflicting priorities. With the inevitable arguments over where research, money, training and equipment, should be concentrated, could a unified European cancer society ever be a runner? Bartelink, who as President of FECS speaks as somewhat of a father figure, has little doubt.

"This is really the strong argument for the new society. Because this debate should happen inside the society. It is much better to have this multidisciplinary approach within the board or wherever, rather than have medical oncologists say 'all patients need Herceptin', and two days later ESTRO says 'we need modern linear accelerators' and ESSO says 'all hospitals need modern laparoscopic surgery'. That would be a disaster, because none of the three will get the money."

The question for the FECS societies is who will be the dominant voice? Will everyone have an equal say, or will some end up trapped, with neither power nor profile, within a European ASCO?

Eggermont, from the EORTC, acknowledges this concern, particularly among smaller organisations, but argues that it is when each society fights for itself that only the most powerful voices are heard. "I think that precisely the smaller organisations – for instance the scientists in the EACR, or the surgeons – have everything to gain from the creation of a European cancer society, because hardnosed discussions and scientists will drive the agenda. I don't think those discussions would necessarily be dominated by medical oncologists. They would be dominated by realistic priority setting, by agreeing that everything will be science and evidence driven. It is a much better platform to create a political and representative agenda."

Bartelink is clear that most European oncologists do not want to adopt the ASCO model or to single out medical oncologists as contributing the most to progress in cancer treatment. "Let us not forget that surgery and radiotherapy are still the treatments that cure most cancer patients. Progress has come from all the disciplines. Surgeons have developed techniques that are less mutilating, radiation oncologists have significantly improved their technology, producing less severe side-effects, and higher cure rates, and, of course, medical oncology, thanks to new research developments, has contributed too."

Despite these assurances and Kosmidis's insistence that ESMO has no wish to eclipse other disciplines, many see it as inevitable that money and influence from close ties with industry will make ESMO top dog in a single organisation. Whether that turns out to be the case, depends in part on the hard bargaining that is still going on within the Federation to determine how much autonomy and financial resources different disciplines will have, and how the leadership of the proposed society will be determined.

Lex Eggermont: A single European cancer society will set realistic, science-driven evidence-based priorities. The smaller FECS societies have most to gain

Getting this right could set the scene for the blossoming of a multidisciplinary organ-specialist approach, and give Europe's cancer professionals a unified and powerful voice that can secure desperately needed investments in research and services. Getting it wrong could set back the cause of a truly multidisciplinary approach that recognises that progress in cancer care means a great deal more than new and better drugs.

"It is when each society fights for itself that only the most powerful voices are heard"

Cancer vaccines edge towards success

Richard Harrop* and Stuart Naylor*

A number of cancer vaccines are now entering the final stage of clinical development. Are vaccines finally on their way to enjoying mainstream success in the oncology arena?

Over the past decade, vaccination strategies for the treatment of cancer have been investigated with renewed vigour, perhaps catalysed by a greater understanding of tumour immunology and the clinical successes achieved with monoclonal antibody and cytokine-based therapies. However, before vaccines become fully integrated into the arsenal of weapons currently used to treat cancer, they must show not only efficacy but also safety and limited or no toxicity. Recently, a number of cancer vaccines have moved into the stages of development where clinical benefits and good safety profiles can be determined convincingly.

Reports from a number of Phase II and Phase III studies suggest cancer vaccines are not only well-tolerated but that they are also meeting clinical endpoints, ranging from significant tumour responses to improvements in median survival time. Results from such trials build on a significant body of Phase I clinical data which suggest that, in general, this class of therapeutic is safe and that the attributed adverse event rate is low. Cancer vaccines that have such a safety profile may be readily integrated into current standard-of-care regimens, particularly in the first-line setting where combination strategies prevail over monotherapies.

Targeted vs non-specific

Cancer immunotherapies can broadly be divided into two categories: tumour-specific and highly-targeted products, for example vaccines or antibodies that target a specific tumour antigen, and therapies which modulate the immune system in a non-tumour-specific way. An example of the latter is BCG, which has been used for many years in the treatment of bladder cancer and has been shown to provide superior benefits over chemotherapy regimens in patients with a high risk of progression. While the precise mode of action of the treatment is not known, it is accepted that it has an effect on the immune system.

Likewise, the cytokines IL-2 (interleukin 2) and IFNa (interferon α) have found widespread use in the treatment of different malignancies, such as renal cancer and melanoma, yet they offer only modest benefits and frequently lead to toxic side-effects.

In between these two approaches lie cell-based therapies, in which whole tumour cells or cell extracts are used as the immunogen. While tumour-specific immune responses may be induced, the precise target(s) of the response is not usually known. Furthermore, immune responses against other common tissue antigens may also be induced. Despite the lack of fine specificity of the immune response induced and the labour involved in the production of autologous, cell-based therapies, a number of products have completed Phase II and Phase III trials with promising results.

The explosion in the identification of tumour-associated antigens (TAAs) in multiple cancer types which occurred in the 1990s represented a critical phase in the ability to apply tumour immunology research to the development of immunotherapy strategies. This discovery enabled the development of targeted treatments and allayed some of the safety concerns over the deleterious autoimmune

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KAREN KASMAUSKI / CORBIS / CONTRASTO

A number of studies suggest cancer vaccines are not only well-tolerated but meet clinical endpoints

reactions that can result from less specific approaches. The successful targeting of specific tumour antigens in vivo has been exemplified by the use of monoclonal antibodies. Although they failed to live up to their promise in the 1980s, they have since enjoyed a renaissance in the treatment of different cancers, and there are currently eight therapeutic antibodies approved by the Food and Drug Administration (FDA) for sale in the US. Campath (alemtuzumab), Rituxan (rituximab), Herceptin (trastuzumab), Mylotarg (gemtuzumab ozogamicin), Zevalin (ibritumomab tiuxetan), Bexxar (tositumomab), Erbitux (cetuximab) and Avastin (bevacizumab) achieved total sales in excess of US$3 billion in 2004.

While the success of monoclonal

antibody therapies cannot be denied, other targeted approaches are now waiting in the wings, including vaccination. Unlike monoclonal antibodies, which are usually delivered as a bolus infusion, a vaccine's therapeutic potential has to be transduced through multiple biological steps within each patient before any clinical benefit is realised. This offers both advantages and disadvantages over the more direct effects of infused monoclonal antibody therapies. On the positive side, a vaccine-based approach:

- Induces a broad polyclonal cellular and humoral immune response
- Leads to a response of potentially greater longevity, requiring fewer injections
- Does not require 'humanisation' of the immune response, unlike the use of monoclonal antibody therapies, which are usually of murine origin
- Costs less

However, success is dependent on the induction of a potent and 'appropriate' immune response in a patient group that may be immuno-compromised. Furthermore, an efficacious response may take a month or more to induce. Despite these drawbacks, a diverse array of cancer vaccines has made the transition from pre-clinical research to clinical development over the past 5–10 years. The positive results now being observed in the clinic owe much to a greater understanding of the immune system, the timing and method used to deliver the therapeutic antigen(s) and the increased sensitivity of monitoring tools.

The main contenders

Given the time and money required to take a product from pre-clinical research to pivotal Phase III clinical trials, only a small number of cancer vaccines have to date progressed to the stage at which efficacy can be established convincingly. However, clinical responses including tumour shrinkage, disease stabilisation and improvements in time-to-disease progression are being reported in controlled trials. And more importantly, statistically significant increases in patient survival have been detected (see Table).

For example, in June 2004, Aphton Corporation of Philadelphia announced the results of a Phase III trial of Insegia, a synthetic peptide, similar to a portion of the hormone Gastrin 17, linked to the diphtheria toxin. The study compared Insegia with placebo in patients with advanced pancreatic cancer and demonstrated a statistically significant increase in patient survival time; 150 days for patients receiving the vaccine compared to 83 days for those on placebo.

And in February 2005, Seattle-based Dendreon announced encouraging results for its immunotherapy product Provenge – autologous dendritic cells loaded ex vivo with a recombinant fusion protein consisting of the TAA prostatic acid phosphatase linked to GM-CSF (granulocyte/macrophage colony-stimulating factor). It was reported that treatment with Provenge significantly improved survival in men with asymptomatic, metastatic androgen-independent (hormone-refractory) prostate cancer when compared to placebo. According to the final three-year intent-to-treat analysis of the randomised Phase III study, patients receiving Dendreon's investigational product showed a 4.5-month improvement in median survival time and a more than three-fold increase in survival after 36 months compared to patients receiving placebo. This is now being followed up with a second Phase III clinical trial, with the objective of confirming recent findings so that FDA approval of Provenge may be sought.

Other immunotherapies have led to positive results in subsets of treated patients, for example, antibody responders in Aphton's Phase II trial of Insegia in colorectal cancer patients, or in multiple, open-label Phase II studies including CancerVax' trials of Canvaxin in melanoma. In the latter study, retrospective analyses showed treatment with Canvaxin, which consists of irradiated cancer cell lines, significantly improved survival of patients with stage IV melanoma. The median overall survival time of 268 patients with the cancer, who received Canvaxin following the surgical removal of their tumours, was 42.4 months compared to 14.3 months for 170 historical control patients who did not receive the vaccine.

Furthermore, a Phase IIb study of Canadian firm Biomira's BLP25 liposome vaccine, a synthetic MUC1 peptide encapsulated in a liposome delivery system, has shown encouraging improvements in overall survival in non-small-cell lung cancer (NSCLC) patients – although it did not quite attain statistical significance – and it has been granted fast-track approval by the FDA.

Another candidate is TroVax, a vaccine based on the TAA 5T4 delivered by the attenuated vaccinia virus, MVA (modified vaccinia Ankara), under investigation by Oxford BioMedica in the UK.

A recent announcement reported interim data from two Phase II clinical trials in which TroVax was administered in combination with chemotherapy to patients with late-stage colorectal cancer.

Immune responses specific to antigen 5T4 were observed in 100%

of patients who were suitable for analysis. This observation is particularly encouraging given that a retrospective statistical analysis of data collated from a Phase I/II study showed a highly significant correlation between the strength of 5T4-specific immune responses and time-to-disease progression.

The following immunotherapies are also in late-stage clinical development: Oncophage from Antigenics in New York, PANVAC-VF from Therion Biologics in Cambridge, Massachusetts, and TG4010 (MVA-MUC1-IL2) from Transgene in Strasbourg, France.

Tempered expectations

Cancer vaccine strategies are often at odds with classical clinical development approaches. For example, they are usually trialled in potentially refractory patient groups in which the ability to galvanise an immune response may well be compromised. And the decision as to where a cancer vaccine is best placed as a therapeutic is a difficult one. Scientifically, the adjuvant setting, in which disease burden is minimal, may well represent the optimal slot to detect clinical benefits. However, it requires a bold decision to commit to this type of study, because large patient numbers are required and clinical endpoints are protracted. Financially, this translates to trials that are exceptionally expensive to conduct and that take many years to yield results, and this is problematic, especially for biotech companies. The selection of both indication and setting, whether adjuvant, first-line or second-line treatment, has to balance the speed in reaching clinical endpoints with the time needed for the immune response to become effective in 'disease management'.

The expectation that vaccines will cure cancer may have to be tempered in certain indications and settings. While tumour regressions have been observed in a number of clinical trials, stabilisation of disease leading to enhanced survival may be a more realistic expectation in patients with large tumour burdens or with rapidly growing cancers.

Despite the challenges, this is an exciting time for the cancer vaccine investigational arena. Results from some of the Phase III trials, such as studies on Canvaxin, GVAX and PANVAC-VF should be available this year or early 2006.

If the primary objectives are met, product registration could follow within a year or two.

Furthermore, important advances are being made in the search for surrogate markers and the ability to predict whether individual patients are likely to respond to a specific treatment. Such information will help to refine the design of clinical trial protocols and target patients who are more likely to gain benefit from the immunotherapy. Subsequently, it is hoped that cancer vaccines will soon become commonplace alongside surgery, chemotherapy and radiotherapy for the treatment and management of cancer.

SELECTED CANCER VACCINES IN LATE-STAGE CLINICAL DEVELOPMENT

Company	Product name	Indication	Trial stage	Trial status	Survival benefit
Antigenics	Oncophage	Renal	Phase III	Part I closed	Not yet available
Aphton	Insegia (G17DT)	Pancreatic[1]	Phase III	Completed	Increase in overall survival[2]
		Pancreatic	Phase III	Completed	Yes (statistically significant)
		Colorectal	Phase II	Completed	Increase in overall survival[2]
Biomira	Theratope	Breast	Phase III	Completed	None
	BLP25	NSCLC	Phase IIb	Completed	Yes (but not statistically significant)
CancerVax	Canvaxin	Melanoma	Phase III	Closed	Not yet available[3]
Cell Genesys	GVAX	Prostate	Phase III	Active	Not yet available
Dendreon	Provenge	Prostate	Phase III	Completed	Yes (statistically significant)
Onyvax	Onyvax-P	Prostate	Phase II	Closed	Not yet available
Oxford BioMedica	TroVax	Colorectal	Phase II	Closed	Not yet available
		Renal	Phase II	Active	Not yet available
Therion Biologics	PANVAC-VF	Pancreas	Phase III	Active	Not yet available
Transgene	TG4010	NSCLC	Phase II	Active	Not yet available

NSCLC – non-small-cell lung cancer [1]With/without chemotherapy [2]In antibody-positive patients [3]Encouraging open-label Phase II studies

Green is the new black

Edzard Ernst*

It enhances survival in ovarian and prostate cancer patients and protects their hearts against damage from chemotherapy drugs. Could green tea be a new wonder drug?

IN Japan, 5.5 billion bottles of green tea were consumed last year. Yet in Europe, green tea is drunk by few. Which is a pity, because it is probably the healthiest choice. Like black tea, green tea is made from the leaves of the tea plant *Camellia sinensis*. The difference is essentially that, for black tea, the leaves are fermented, while for green tea they are not. Green tea therefore contains plenty more chemicals called polyphenols. These are powerful antioxidants with exotic names, such as catechins, epicatechin, catechins gallate and epigallocatechin gallate. It is these ingredients that may make green tea good for our health.

Years ago, epidemiologists noted that cancer rates in populations that consume green tea were lower than expected. We should not get too excited about such findings. For instance, tea drinkers could also be avoiding things that cause cancer or have a lifestyle that protects them. But encouraging results about green tea kept coming in and eventually formed a compelling body of evidence. The curiosity snowballed and, currently, research into the health aspects of green tea is buoyant.

Studies in test tubes show that the ingredients of green tea inhibit tumour growth and cause the death of cancer cells. In animal experiments, green tea impedes the development of chemically induced cancers. Some green tea ingredients seem to enhance the effect of anticancer drugs. Other compounds protect our organs against the damage that cancer drugs can have, for instance, on the heart. Taken alongside chemotherapy, green tea could maximise the benefits of such drugs and minimise their risks.

These effects may be valuable for a range of cancers. Importantly, they are supported not just by one or two investigations, but by dozens of studies from around the world.

But the proof of the pudding is in the eating.

Do we have data from clinical trials, or is all this based on lab experiments? So far few such studies have been completed. A rare exception is a prospective investigation from China of 254 women with ovarian cancer. While 78% of the green tea drinkers survived for longer than three years, the figure was only 48% for the abstainers. The authors of this study therefore believe that "increasing the consumption of green tea ... may enhance epithelial ovarian cancer survival." Another analysis found similar effects for sufferers of prostate cancer.

Antioxidants in green tea are not only important for cancer, they might also play a role in cardiovascular disease. Regular green tea consumption normalises lipid metabolism, reduces blood pressure, slightly lowers body weight, stabilises glucose metabolism in diabetes patients, and might even neutralise some effects of smoking. Collectively these effects are likely to amount to a significant protection from heart disease, stroke and other cardiovascular problems.

However, clinical trials are again scarce. A Japanese team observed 203 patients who underwent a coronary angioplasty. Of these, 109 had coronary artery disease while the rest had normal coronaries. Patients with normal coronary arteries consumed significantly more green tea compared to those who had diseased

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TIZIANA AND GIANNI BALDIZZONE / CORBIS / CONTRASTO

In a Chinese study, 78% of green tea drinkers, but only 48% of abstainers, were alive at three years

coronary arteries. The authors were optimistic: "The more green tea patients consume, the less likely they are to have coronary artery disease." Before you rush out to buy a car load of green tea, a word of caution. All these findings are encouraging but, to be sure, we really need the results of clinical trials. These will take a while to come through. The good news is that green tea is delicious and refreshing. The bad news is that to match the dose used in the research studies, you need to drink up to 12 cups a day.

Let's be honest...

Vaclav Havel

Playwright, dissident, and first President of post-communist Czechoslovakia, Vaclav Havel lost his first wife to cancer in 1996, and was himself diagnosed with lung cancer later that same year. He'd survived years of suppression and imprisonment and had begun to lead his country into a new era. How did Havel now cope with this new challenge? *Cancer World* asked him.

I have to say that my cancer was surgically removed almost as soon as diagnosed, so I really did not experience cancer as a disease. Whatever experience I have is related to its accompanying effects or indirect consequences. A little tumour was discovered at a certain time – and basically by coincidence – in my lungs, which I did not feel or know about and which did not hurt. However, the tumour was very dangerous, growing fast, every day mattered, and therefore I was soon operated.

The surgery went well; it is true I lost a piece of my lung, but the tumour was removed and there were no remnants, metastases or other consequences. Nevertheless, the reduced size of lungs has resulted in a long series of secondary pulmonary ailments and I have also suffered from diverticulitis, which is an intestinal disease. I have become a man who is no longer quite healthy, I have even been through times when I was on the verge of death, and I must forever be very, very careful.

With most serious ailments, it is always very important to have someone close, who gives the patient strength. In my case, it was my wife who gave me strength and helped me, and who was with me through everything.

As for medical care, I observed one thing: it is very advisable to openly discuss such serious diseases with the patient from the very beginning. Unfortunately, the practice in our country – contrary, for example, to America – is not to reveal anything to the patient, particularly if he or she suffers from a serious disease.

The reasons are understandable, of course, but my personal experience is that you are stronger if you know what you are suffering from. The knowledge helps the patient face the disease, as opposed to a situation when he or she is drowning in a bottomless sea of secrets and concealment. I have also found that it is good if doctors can cooperate as colleagues and respect one another. Prestige and envy games are the worst thing a treated patient can encounter, and they invariably turn against the patient at the end of the day.

Doctors are human beings just like anyone else, with all human virtues and vices, they are not something special, but my experience indicates that the more communicative a doctor is, the better he or she gets along with other doctors or nurses, seeks or gives advice, compares opinions or defends his or her position, the better for the patient.

"The more doctors feel able to seek advice and compare opinions, the better for the patient"

With his second wife, Dagmar Veskernova (Dasa). Havel credits her with saving his life. Following surgery to remove half his right lung, he was on a ventilator in intensive care when he seemed to be choking. Dasa was there on a visit, and it was she who summoned help. A few weeks later, Dasa and Vaclav Havel were married

Vaclav Havel

Living in truth

Telling it as it is has always been more than just a moral imperative for Havel. It is a political weapon that he used first in the 1960s as a playwright who helped propel Czechoslovakia towards the political reforms and cultural revival that became known as the Prague Spring. After the invasion and occupation of his country by Warsaw Pact forces in 1968, and the subsequent political clampdown, Havel would argue that dissent means "living in truth" – a view not always popular with fellow dissenters who advocated a more ideologically based resistance. This same emphasis on personal honesty and integrity was later to infuriate his political aides and allies when, as Czechoslovakia's first post-communist President, he insisted on voicing his own self doubts in public. Apparently he believes there are those in the medical profession who might also benefit from a greater willingness to admit they may not have all the answers and to seek advice from others.

A life in dates

1936 Havel is born in Prague

1963–1968 His early plays – *The Garden Party*, *The Memorandum*, *The Increased Difficulty of Concentration* – focus on the absurdity and stifling 'automatism' of the regime

1968 In April, the 'Prague Spring', demands for a democratic electoral system and freedom of assembly and expression are met. In August, Czechoslovakia is invaded by Warsaw Pact forces. There is a clampdown on dissent. Havel's plays are banned

1975 Havel writes an open letter to the President highlighting the social ills of his country

1977 He co-founds Charter 77, a human rights initiative, which becomes a focus of dissent

1977–1989 Havel is repeatedly arrested. In all, he spends almost five years in prison

1989 The Civic Forum, a coalition of opposition groups pressing for democratic reforms, is established on November 19. The next day Havel addresses a crowd of half a million people in the centre of Prague and tells them to keep demonstrating. The Communist Party agrees to form a coalition government with the Civic Forum. Havel is elected interim President

1990 Havel is elected first President of post-communist Czechoslovakia

1993 After Slovakia gets its independence, Havel is elected President of the new Czech Republic

1996 Havel's wife, Olga Splíchalová, dies of cancer. Later that year Havel is himself diagnosed with lung cancer and nearly dies following an operation to remove half his right lung

1998 Havel is re-elected to the Presidency and serves a full five-year term, despite his health problems. In contrast to many figures who led their countries out of the communist era, Havel still retains immense personal respect and authority both at home and abroad.

All in the blood

How the Pavlovsky family put Buenos Aires on the haematological map

➜ Peter McIntyre

Despite being home to three generations of Pavlovskys – Alfredo, the founder, Santiago, now medical director, and Astrid a fellow – Fundaleu is no family firm. On the contrary, it was the Pavlovskys' commitment to looking outward to international networks that made it possible to develop this world-class leukaemia centre in Buenos Aires.

Most doctors remember their early successes, so it is no surprise that Santiago Pavlovsky can recall the first adult patient he cured of leukaemia. What is more remarkable is that he still takes a close interest in his first patient, 37 years later.

The year was 1968. At 27, Pavlovsky, back in Argentina from Europe, was scarcely older than his patient. The 23-year-old man had just married, and the diagnosis of acute lymphoblastic leukaemia must have sounded like a death sentence.

Pavlovsky could offer hope. He had recently attended the first international convention on daunorubicin and he treated his patient with this new cytotoxic drug. Being unsure of the side-effects, he asked the young couple to ensure that the wife did not become pregnant. Of course, she did. Pavlovsky and the family waited anxiously to see what would happen to father and baby.

All turned out well. The father went into remission that turned into a cure, and his wife delivered a healthy baby boy. The couple had four more children and the firstborn has children of his own. Now aged 60, the patient is still well. Pavlovsky said, "I see him at least once a year. He has never had a recurrence. This was the first adult patient I ever saw cured."

This quietly spoken Argentinean is very aware that this one life saved has led to a whole extended family. A sense of family is part of his personal identity. Fundaleu (Foundation Against Leukaemia), of which he is medical director in Buenos Aires, was founded by his father. His identical twin bother, Miguel, is also a distinguished haematologist in Argentina, and his daughter Astrid works alongside him.

Santiago Pavlovsky winces at the suggestion of a dynasty. He is as proud of dissuading his son (a successful economist) from following him into medicine, as he is proud that his daughter has done so. "Not dynasty, but probably destiny," he says with a smile.

Pavlovsky also has a commitment to internationalism. He sees co-operation between specialists and centres as ever more important to provide sufficient research data on rare cancers and different oncogenes.

Santiago Pavlovsky (seated at the table) with his team of doctors, nurses, scientists and technicians at Fundaleu in Buenos Aires. Standing at his left shoulder is his daughter Astrid

His grandfather, Alejandro Pavlovsky, was born on the banks of the Don in Rostok, in what was then Russia (now Ukraine). Russian Jews were subject to discrimination and pogroms by the Cossacks. Many converted to Catholicism and left. At the age of 18, Alejandro joined older brothers and sisters in Argentina, where he worked his way up to become chief executive of the Buenos Aires municipal authority and married a woman from Mendoza. Santiago's father, Alfredo, was the tenth of their 11 children.

Alfredo graduated from the University of Buenos Aires in 1931, and his PhD thesis on the detection of malignancy made him famous almost immediately.

Santiago says, "His idea was to differentiate a lymph node that was tuberculosis, which was very common, from a lymph node that was malignant disease. They looked the same. My father used a needle to take an aspiration and put the cells in a smear and he looked at them under the microscope. He compared what he saw with what the pathologists said in their report until he was able to differentiate them based on what he could see."

Alfredo won a top prize in Argentina, and Adolfo Ferrata, 'the father of Italian haematology', was so impressed that he included the thesis as a chapter in his text book in 1936.

Alfredo Pavlovsky spent a lifetime treating haematological diseases. He was one of the founders of the International Society of Hematology in Paris after the war, and in 1954 was President of the Fourth International Congress of Hematology in Mar del Plata, Argentina.

Blood brothers

He and his wife, Maria, had five children, including identical twins Santiago and Miguel in 1941. The twins went to school together (where they could swap classes without their teachers knowing), and learnt to ride horses together. Both became haematologists. Both work mainly in non-profit organisations. The difference is that Miguel works on coagulation, thrombosis

Santiago Pavlovsky winces at the suggestion of a dynasty – it is more a case of destiny, he says

He worked tirelessly to collect data and spread treatment protocols across the country

and vascular disorders, while Santiago specialises in haematological malignancies.

Santiago began working at the Haematology Research Institute of the National Academy of Medicine in Argentina, where his father was Director. He married young and, with his wife Tatiana, left for France to do his fellowship. Tatiana spoke good French and English and was quickly able to get work in Paris. Pavlovsky recalls, "She was my economic support because my fellowship was very lowly paid, and difficult to live on for one, much less two. Her salary was three times my fellowship."

Professionally, Pavlovsky struck gold at St Louis Hospital, Paris, joining Jean Bernard, then the leading haematologist in Europe, later a French academician, and still alive and lucid at the age of 98. "I had two big inspirations in my career: one was my father, the other was Jean Bernard. He was the big professor type. He ran the best haematology department in Europe and was very well known all over the world. Jean Bernard was very strong in leukaemias and later in lymphomas. I admired him because he started collaboration with the Americans, trialling drugs in acute lymphoblastic leukaemia [ALL] in children."

These Cancer and Acute Leukaemia Group B (CALGB) trials showed the effectiveness of anthracyclines; 40 years later, daunorubicin is still a first-line treatment for ALL.

Pavlovsky returned to Buenos Aires in 1967, to create the oncohaematology department at his father's institute. Other young doctors and scientists were also returning. With Federico Sackmann at the Children's Hospital in Buenos Aires, and other colleagues, Pavlovsky launched the Argentinean Group for the Treatment of Acute Leukaemia (GATLA).

Four institutions grew to 25. They began by copying the work of Bernard, but quickly built their own expertise.

Pavlovsky recruited patients to clinical trials and built a statistics department that could turn data into a coherent story. As chairman of GATLA, he worked tirelessly to collect data and spread treatment protocols across the country.

"We held two big meetings a year in Buenos Aires to which all the physicians from around the country came. Most of them were very young at that time and very enthusiastic about doing clinical trials. We were learning together. Argentina is a huge country with long distances. In the beginning most of the children came to Buenos Aires to be cured, but later many physicians who had trained in Buenos Aires went back to their provinces to treat the children with this new national protocol.

"At that time, in the late 1960s, to tell a patient that the disease could be cured was blasphemy. In the 1970s we started to mention the word 'cure' in relation to acute lymphoblastic leukaemia in children."

By 1973, the team was confident enough to co-organise in Cuba the first Latin American cooperative group on haematology. This inspired clinical trials over a wide range of disorders. Pavlovsky became chairman of the group looking at haematological malignancies, bringing together data from Argentina, Brazil, Chile, Costa Rica, Cuba, Uruguay and Venezuela, agreeing protocols for treatment and publishing in international and peer review journals. The Latin America group developed protocols for childhood leukaemia, Hodgkin's disease, lymphoma and multiple myeloma.

The children's hospitals were good and the paediatricians and young scientists were enthusiastic. "Everybody was looking for new things. The idea of doing a clinical trial was new. The idea of curing a cancer patient was new. Older haematologists had very little knowledge of chemotherapy. For them the most important thing was a diagnosis because there was nothing

Alfredo and Maria Pavlovsky with their children. In the centre picture, Santiago is second from the left with his twin brother Miguel

They published in leading oncology journals, struggling as much with the English as the science

they could offer as a cure. They were very happy for this new generation to take care of this job."

Before computers, fax, couriers and e-mail they punched holes in cards to record data, typed up reports on manual typewriters and circulated drafts through slow and unreliable postal services. They published in leading international oncology journals, often struggling as much with the English as they did with the science.

In 1979 the Argentinean group joined a collaborative cancer treatment research programme (CCTRP) sponsored by the US National Cancer Institute. This paired centres in the US with the National Cancer Institutes in Mexico, Brazil, Peru, Uruguay, Venezuela and Chile. The Cancer Research Institute in Buenos Aires was twinned with the Lombardi Cancer Center in Georgetown University, Washington DC.

In 1983, Pavlovsky became co-ordinator of the CCTRP programme and moved to Washington, where he was also cancer advisor to the Pan-American Health Organization (PAHO). By the time he returned to Argentina in 1986, his father had died and his generation had become the established leaders of cancer research and treatment.

Military dictatorship, a disastrous war with the UK, an economic crisis and 'Reagonomics' had a destructive impact on public services in Latin America, and it became more difficult to carry out collaborative work.

A CENTRE OF EXCELLENCE

In the 1950s, Alfredo Pavlovsky had founded Fundaleu, the Foundation Against Leukaemia, to fund and carry out applied clinical research. Now in the 1980s Santiago Pavlovsky began to build this organisation into a centre of excel-

His scientists can now identify the molecular structure of cancers and pinpoint the oncogenes

lence. He brought in the best doctors he could find and raised money from private companies and rich individuals. In July 1989, Fundaleu opened the Angelica Ocampo Research and Treatment Centre, dedicated to leukaemia.

In 1991 Fundaleu was one of the first centres in Latin America to start stem cell transplantation to treat leukaemia, myeloma and lymphoma. The team carried out 820 stem cell transplants over the following 14 years, mainly taken from peripheral blood. This required careful selection of patients. Pavlovsky said: "You have to avoid the patients in the late stage because they cannot be cured. We tried to educate the medical profession to transfer the patient early enough to be able to use the transplant."

The reputation of Fundaleu grew throughout the 1990s. In October 2003, it opened an outpatient department complete with molecular biology, flow cytometry, pathology and bacteriology laboratories. Pavlovsky says that his scientists can now identify the molecular structure of cancers and pinpoint the oncogenes for individual patients.

"The objective is not only to achieve clinical remission but molecular remission. Patients who show complete molecular remission have more chance of being cured. If you are able to identify an oncogene that causes the disease you can follow whether this oncogene disappears or at least is reduced many times. If the oncogenes do not decline the disease will come back; if the oncogene disappears they will be in remission for ever."

Fundaleu sees 700 new patients a year and has 7,600 patient visits. Only 20% of patients are children now that children's hospitals offer excellent treatment. The team carries out stem cell transplants on patients of all ages, including patients over 70 years old.

Most patients receive chemotherapy as outpatients, although a patient who has an infection or a reaction to chemotherapy can stay for 24 hours without being admitted to the hospital. Patients also receive round-the-clock telephone support.

Pavlovsky was determined to attract top-line doctors, nurses and scientists. "Fundaleu is now paying good salaries to doctors, nurses, technicians and scientists and providing good equipment for them to do research. I think that Fundaleu is now an inspiration for many other institutions in the way that we combine clinical practice and research."

Fundaleu employs only graduate nurses, most of whom have a post-graduate qualification in cancer nursing. "We probably have one of the best rates of nurses to patients in the world – one nurse for every two or three patients. All our nurses can deliver intensive care in any of our rooms. Hundreds of nurses come here to learn how to take care of patients with chemotherapy and our oncology nurses do a lot of teaching around the country.

"We educate our nurses to learn about the treatments, side-effects of chemotherapy, and the doses they have to deliver. Well-trained nurses provide a safety net. If they know the doses of the drug and they know the side-effects, they can avert any prescription mistakes by the physician."

Aged 63, Pavlovsky plans to work for another seven years, before focusing on family and

"Fundaleu is an inspiration for others in the way that we combine clinical practice and research"

Santiago Pavlovsky (with the whip) in competition in Argentina with carriage and horses

With his wife, Tatiana, at the meeting of the Challenge Fund in Rome in January 2005

horses in retirement. But retirement must wait. Pavlovsky, who was named Doctor of the Year in 2000 by the Argentine Ministry of Health, is driven by the need to encourage young doctors to support international research. "Clinical research means you do not only follow a protocol but you collect data and help the statistician to evaluate the data, and present the data in a meeting and, last and most important, you publish the data. If you have 800 cases with good information on treatment, outcomes and side-effects, and you enter an international meta-analysis, your 800 patients can become 20,000."

Fundaleu is collaborating in a study organised from Spain, treating acute promyelocytic leukaemia (APL) with ATRA (tretinoin), a drug developed from Chinese herbal medicine. Fundaleu is part of the extra-nodal lymphoma study group (IELSG) run by Franco Cavalli at the Oncology Institute of Southern Switzerland in Bellinzona. This looks at very rare lymphomas which affect one site, such as the testes or stomach, where international collaboration is the only way to collect enough data. Evidence from Fundaleu was included in international Cochrane Collaboration reviews of multiple myeloma, Hodgkin's lymphoma and acute myelogenous leukaemia (AML). Santiago's daughter Astrid has completed her second year of fellowship at Fundaleu. Her father believes that the changes in her professional lifetime will be even more dramatic than in his own.

"In my lifetime I have passed from practically no cure for haematological malignancies to around 80% of the children with ALL and 80% of Hodgkin's lymphoma and around 50% of the non-Hodgkin's lymphoma. I have seen a doubling of the life of multiple myeloma and chronic lymphocytic leukaemia [CLL].

"Now there is a breakthrough in chronic myelocytic leukaemia [CML]. Glivec [imatinib] is the first drug in the world that appears to be killing the neoplastic cells without killing normal cells. Each year, the news improves. More than 80% of patients who were treated four years ago are still alive without disease. It is fantastic.

"In my daughter's time, I do not think there will be one drug to cure all neoplastic diseases, but there will be other drugs targeted at specific diseases. I am sure that Astrid and her generation will see more and faster changes than I have seen."

"I'm sure that Astrid and her generation will see more and faster changes than I have seen"

ESMO Minimum Clinical Recommendations

Inadequate diagnostics, inappropriate treatment and poor follow-up deny cancer patients their best chance of survival. Whether you work in a hospital in rural Hungary or at the Jules Bordet in Brussels, ESMO's updated recommendations spell out what you need to do to ensure your patients receive an acceptable standard of care.

The European Society for Medical Oncology (ESMO) is continuing to expand and update its internationally respected collection of Minimum Clinical Recommendations (MCRs) for the treatment of cancer. The supplement to *Annals of Oncology* vol 16, 2005, contains 35 updated MCRs, freely available for oncologists around the world.

Each of the MCRs provides vital, evidence-based information for physicians, including the incidence of the malignancy, diagnostic criteria, staging of disease and risk assessment, treatment plans and follow-up. They aim to provide the user with a set of requirements for a basic standard of care that ESMO considers necessary in European countries. They are not designed to replace extensive clinical practice guidelines or review articles.

To keep abreast of the rapid changes in the field of medical oncology, each MCR undergoes an annual update. The ESMO Guidelines Task Force invites a coordinator (author) to draft an MCR on a specific topic, according to a standard outline; the draft is revised with the input of the ESMO Guidelines Task Force and subsequently submitted to the ESMO Faculty for review; and finally, comments from the Faculty are considered by the Task Force and a final version is prepared for publication. Rolf Stahel, chair of the ESMO Guidelines Task Force, says "The minimum clinical recommendations are an important expression of ESMO's mission to disseminate knowledge, in order to maintain a high common standard in medical practice for cancer patients." He adds that they also help support negotiations with politicians, administrators, and insurance companies about what level of care should be made available, and are an important part of the development of medical oncology as a specialty.

Vesa Kataja, a Finnish medical oncologist who sits on ESMO's Guidelines Task Force, says that the great thing about the MCRs is they are easy to use. "Finland is a country with a high tax rate and well-organised national healthcare, which for many years has utilised national guidelines on different disease entities, including several in oncology. In a situation like this, one would think that there is no cause for even more guidelines. However, the national

The ESMO Guidelines Task Force. Rolf Stahel (chair) is seated at the far end on the left; Vesa Kataja is sitting on the right-hand side, third from the front

guidelines, although elaborate in quality, up-to-date and very much evidence-based, are somewhat difficult to use in everyday practice. Thus the ESMO MCRs, being clinical practice guidelines and a practical synthesis of all evidence within a given field, have found their way to becoming a handy tool for many Finnish colleagues, even outside the oncology field."

So handy, in fact, that many of Kataja's colleagues want them literally in their hands. "Although everyone working in the Finnish healthcare system has access to the Internet and the ESMO website, some 50 folders containing the MCRs were practically ripped out of my hands when I presented them at a meeting," he said. Kataja takes every opportunity to promote discussion of the ESMO MCRs, for instance at the Meeting for Residents in Specialist Training and the Annual Meeting of the Finnish Society of Oncology. "I have recommended them as reading for medical students in preparation for the examination in oncology, for residents and other colleagues in response to consultation – I told them 'see what the ESMO MCR says on the subject' – and referred to them in my lectures and presentations. There is no doubt in my mind that in these days of information influx, the ESMO MCRs, with their practical approach, will find a steady place in everyday clinical life – all over Europe."

As important as practicality is credibility. It is inevitable that during the elaboration of the MCRs, controversial issues on diagnostic and therapeutic recommendations regularly arise. Stahel is keen to emphasise that the published Recommendations represent an ongoing process that needs the participation of all ESMO members. To encourage this, and to give some insight into some of the more finely balanced decisions, the Guidelines Task Force plans to publish controversies on ESMO MCRs in future issues of *Annals of Oncology*.

UPDATED RECOMMENDATIONS

Updated MCRs are available at www.esmo.org for

Diagnosis, treatment/adjuvant treatment and follow-up of:

- primary breast cancer; locally recurrent or metastatic breast cancer
- epithelial ovarian carcinoma
- colon cancer; advanced colorectal cancer; rectal cancer
- gastric cancer; pancreatic cancer; oesophageal cancer
- non-small-cell lung cancer; small-cell lung cancer
- malignant pleural mesothelioma
- prostate cancer
- mixed or non-seminomatous germ cell tumours
- testicular seminoma
- invasive bladder cancer
- acute myeloblastic leukaemia in adult patients; chronic lymphocytic leukaemia
- multiple myeloma
- chronic myelogenous leukaemia
- Hodgkin's disease
- follicular lymphoma
- newly diagnosed large cell non-Hodgkin's lymphoma; relapsed large cell non-Hodgkin's lymphoma
- squamous cell carcinoma of the head and neck
- malignant glioma
- cutaneous malignant melanoma
- soft tissue sarcomas; osteosarcoma; Ewing's sarcoma of bone
- cancers of unknown primary site

and for

- prophylaxis of chemotherapy-induced nausea and vomiting
- application of haematopoietic growth factors
- management of cancer pain

MEPs join forces against cancer

Anna Wagstaff

Europe could do so much more to boost cancer research and ensure all its citizens get good quality treatment. Now a group of politicians has got together to make sure it does.

A group of around 30 Members of the European Parliament (MEPs) have got together to launch MEPs Against Cancer. The new forum (which abbreviates to MAC) describes itself as an all-party informal group, committed to promoting action on cancer as an EU priority, and harnessing European health policy to that end.

The forum is headed up by a triumvirate – Alojz Peterle, Adamos Adamou and Liz Lynne – that includes patient, oncologist and campaigner, and is representative of both the regions of Europe and the political spectrum of the Parliament.

Peterle, who spearheaded the formation of MAC, comes from Slovenia. He was prime minister when Slovenia declared its independence from the former Yugoslavia in 1991, and has spent the last couple of years helping to hammer out the ill-fated EU constitution. Four years ago he was diagnosed with prostate cancer, which he fought by making radical changes to his lifestyle. He has since been declared free of the disease. Peterle believes widespread negative attitudes that see cancer as an automatic death sentence can fatally undermine the determination of patients to survive and sap the political will to improve standards of care. "My personal priority is to get more and more awareness among MEPs in the European Parliament and also among MPs in the Member States, because with legislation we can influence a lot."

Adamou comes from Cyprus, and is an oncologist by profession. He is a member of the Cyprus Anticancer Association, and has a track record of urging political action on cancer. His priority is to ensure that every European cancer patient has an equal chance of an early diagnosis and good-quality treatment. He argues that the most dramatic improvements in the near future will be made through improved structuring of cancer care services, and wants to see MAC contributing to this goal. "I believe that the MEPs Against Cancer forum will help raise awareness on an issue that affects all of us directly or indirectly, and will aid in the establishment of European standards for cancer prevention and treatment."

MEPs Against Cancer can be contacted via the co-chairs: Adamos Adamou, aadamou@europarl.eu.int; Liz Lynne, elynne@europarl.eu.int; and Alojz Peterle, apeterle@europarl.eu.int; or through the secretariat: hildrun.sundseth@ecpc-online.org

MEPs Against Cancer is headed by three co-chairs. *From left to right:* Adamos Adamou, Liz Lynne and Alojz Peterle

Liz Lynne comes from the UK, where she has a long history as a member of the national parliament working on health in general and cancer in particular, including as co-chair of the All-Party Breast Cancer Group. She feels MEPs have to take up the fight against cancer, not least because 3 million of their constituents are diagnosed every year and 2 million will die from the disease. "Although I believe health policy should be up to individual Member States, it is important for us in the EU to share best practice in research, treatment and care," she said, giving a special mention also to the need to pressurise governments to aid more research into the disease.

The initiative has been warmly welcomed by the European Cancer Patients Coalition (ECPC), which has offered to run the secretariat. ECPC chairman Lynn Faulds Wood said: "The European Parliament has produced many policies and recommendations which have the capacity to improve the lives of cancer patients across Europe, but we patients know there can be big gaps between policy and putting recommendations into practice. Thousands of lives are being lost unnecessarily to cancer every year, and it is only through our political representatives being prepared to put themselves forward in groups like MAC to campaign for change that we will see major improvements in the way cancer patients are treated."

Peterle hopes that the MEPs in MAC will not only play a legislative role, considering and intervening on the many draft directives that impact in one way or another on cancer, but will also form a bridgehead to their own national governments, which is the level at which many of the key decisions will be taken. The European Council Recommendation on Screening for Cancer, he says, is a case in point. Though the European Commission has adopted the recommendation as a political priority, it cannot insist on its implementation by Member States – that decision will be up to national parliaments.

There are many issues, however, that MEPs will be able to influence directly. Jan G, a cancer patient whose life may have been saved because he fought his way into one of the early imatinib (Glivec) trials, hopes that public access to information about clinical trials in Europe will be one of them.

Jan, who sits on the board of the ECPC, points out that when cancer patients develop resistance to existing drugs, getting early access to an experimental drug could save their life. Though Europe now has a clinical trials database (EudraCT), set up by the European Medicines Agency (EMEA), patients cannot access it to find out about trials they may be eligible for. "It is one of my hopes that MEPs Against Cancer will understand the importance of transparency on basic data on clinical trials for patients," he says.

Whether or not MAC takes up this issue, Peterle is clearly committed to working with patient groups. "I think it is important that MEPs are related more closely with organisations such as the ECPC, because I think those groups should feel the support of politicians. Together we will do more, I'm sure."

Award for journalist who exposed failings in Hungary's cancer services

Viktória Kun, Health Correspondent on the leading Hungarian national daily newspaper *Népszabadság*, is one of two winners* of this year's ACE (Awarding Cancer Enlightenment) Reporters' Award. Here we reprint an article in which she highlights flaws in the country's oncology services that are responsible for some of the worst outcome statistics in Europe.

"My patient was complaining about severe pain in the limbs and arm atrophy. We soon discovered that the continuous pain was caused by a cancer that had spread. The primary tumour had been found in the breast of this middle-aged woman four years ago. At this time it had not spread. She did not get any treatment after her surgery, therefore no efforts were made to prevent what could have been prevented at that time. Another, a young girl – scarcely 20 years old – was referred to me recently with continuous diarrhoea.

On examination we discovered a tumour of her colon, despite the fact that her uterus had been removed only one month previously because of a cancer."

These are just two stories one general practitioner has dealt with over the past few months. Along with the experience of his own wife, they illustrate the significant problems of cancer services in Hungary today.

"My wife was diagnosed with a breast and ovary tumour four years ago. At the time it was thought to be inoperable, and treatment with Taxol was recommended. She was referred to a gynaecologist whose first sentence was: 'You are welcome but there is no Taxol.' I used my contacts to get access to the necessary medicine; however, my wife did not tolerate the chemotherapy very well. It was thought that this was due to an allergy and therefore treatment was stopped immediately and another treatment prescribed. We tried everything. Subsequently, it was discovered that it was not an allergy, but the dose of the medicine was wrong. When my wife was in a very poor

* The other joint winner of the 2005 ACE Reporters Award is Ioanna Soufleri, Science Editor on the Greek national daily newspaper *To Vima*. One of her articles will be reprinted in the next issue of *Cancer World*

„Taxol, az nincs…”

Magyarországon ma a daganatos beteg gyógyulási esélyei rosszabbak, mint akár tőlünk pár száz kilométerre. De még az országon belül sem mindegy, ki és melyik intézetbe kerül. A szakorvosok epidemiológiai válságról beszélnek.

KUN J. VIKTÓRIA

– Karsorvadásra, erős végtagfájdalomra panaszkodott a betegem. Rövid időn belül kiderült, hogy daganatos betegség okozza a folyamatos fájdalmakat. De már nem is csak egy helyen. S mindez nem először. A középkorú hölgy mellében négy évvel ezelőtt már találtak daganatos elváltozást. Igaz, akkor még csak ott. Az operáció után semmilyen utókezelést nem kapott, így nem előzték meg az akkor még megelőzhetőt. Egy másik, alig húszéves fiatal lány a napokban keresett meg azzal, hogy folyamatosan hasmenése van. A vizsgálatok vastagbéldaganatot igazoltak nála, jóllehet egy hónappal korábban távolították el a méhét, ugyancsak rákdiagnózis miatt.

Ez csupán két történet annak a háziorvosnak az utóbbi néhány hónapjából, aki saját feleségével a mai onkológiai ellátás szinte minden alapvető gondját megtapasztalta.

– Emlő- és petefészek-daganatot diagnosztizáltak a feleségemnél, éppen négy éve. Azt mondták, operálni nem lehet, Taxol-kezelést írtak elő neki, s egy nőgyógyászhoz irányítottak, akinek az első mondata az volt: jöjjenek nyugodtan, de Taxol, az nincs. Amikor orvosi kapcsolataim révén eljutottam oda, hogy végül megkaptuk a megfelelő gyógyszert, a kemoterápián a feleségem rosszul lett. Rögtön kijelentették, hogy allergia, úgyhogy a terápiát félbehagyták, majd újabb és újabb készítményeket kapott. Csaknem a teljes kört „végigzongorázták”. Utólag fedezték föl, hogy nem allergiáról volt szó, hanem rosszul adagolták a készítményt. Amikor pedig már nagyon rossz állapotban volt a feleségem, és folyamatosan csapolásra jártunk, elvittem volt évfolyamtársamhoz, aki sebész. Ő úgy döntött: megműti a nejem. Így derült ki, kétéves procedúra után, hogy a tumor műthető. A feleségem most jól van, holott akkor csak hónapokat jósoltak neki.

Dank Magdolna

Kismarton Judit

Magyar Tamás

Ehhez hasonló esetek sorával találkoznak jogvédők, betegszervezetek képviselői vagy a szakemberek. Azaz, hogy nem a megfelelő helyre, s időben kerülnek a segítségre szorulók. Ma a betegek jelentős részét csak akkor látja az onkológus, amikor a daganat már áttétes.

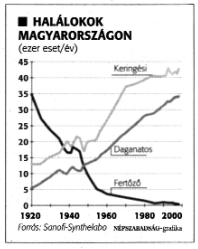
– Petefészekműtéteket az ország szinte valamennyi kórházában végeznek, annak ellenére, hogy a beavatkozás szakmai feltétele a patológiai háttér, radarásul elméletileg kizárólag onkológiai centrumokban engedélyezik az ilyen operációt – mondja dr. Ruzsa Ágnes, a Zala Megyei Kórház onkológiai osztályának vezetője. – Ma bármelyik kiskórház bátran elvégez daganateltávolítást, nemegyszer anélkül, hogy onkológus látná a beteget. Kiveszik a daganatot, lezárják a sebet, majd hazaengedik a gyógyultnak tekintett pácienst – mondja a doktornő, aki szerint alapkövetelmény lenne, hogy a rákbeteg utókezelésre, kemoterápiára kizárólag onkológiai osztályra, centrumba kerüljön. – Másik, szintén nem ritka gyakorlat, hogy „adjunk valamit” felkiáltással, a protokollokat, szakmai előírásokat figyelmen kívül hagyva, nem megfelelő dózisban és időintervallumban adnak valamilyen terápiát. A fontos az, hogy ott maradjon a beteg – állítja Ruzsa Ágnes.

Dr. Thurzó László, a szegedi onkoterápiás klinika vezetője országos felmérést készített a petefészek-daganatok kezeléséről. A vizsgálatok szerint az adott évben mintegy ezerkétszáz felismert és jelentett beteg közül mindössze négyszáznyolcvan kapott ezerhatszáz kemoterápiás kezelést. – A betegek alig harminc-harmincöt százaléka jutott el utókezelésre, azaz részesült szakszerű ellátásban. A többieknek nyoma veszett, elkallódtak a rendszerben. Ez az arány pedig még akkor is lesújtó, ha közöttük vannak idős betegek, akik nagyon rossz állapotban vannak, s emiatt maradnak ki a terápiából – állítja Thurzó László.

Dr. Magyar Tamás, a budapesti Péterfy Sándor utcai Kórház vezető onkológusa egyenesen azt mondja: jelenleg egy daganatos beteg sorsa attól függ, hogy ki észleli először a bajt. Egy rákbeteg minden olyan terápiát, kezelést megkaphat ugyanis, amit bárhol máshol a világon, a hiba elsősorban nem ebben van. – Egy éppen nagykorú lány került hozzánk, akinek kivették a petefészkét. Műtét közben derült ki, hogy rosszindulatú daganata van, ráadásul annak is egy nagyon veszélyes típusa. A leleteit konzultációra még Amerikába is kiküldték, s a vélemények összegzése alapján kapta a terápiát. Ma gyógyult. Ha mindez egy kiskórházban, bármilyen onkológiai háttér nélkül történik, nem él már a lány!

Magyar szerint az elérhető és szükséges diagnosztikai eszközöknek általában mindössze negyven százalékát használják ki egy-egy ráktípus pontos azonosításához. – A kismedencei daganatoknál például kötelező az MR-vizsgálat afelett, hogy pontosan tudjuk, mi a szükséges, leghatékonyabb terápia. Ez most mindössze az esetek felénél történik meg. Jóllehet így legalább ötven százalékkal javulhatnának a gyógyulás esélyei. Ilyen például a tumormarker-vizsgálat: a helyzetet egyértelműen mutatja az a tény, hogy míg ebből a vizsgálatból Magyarországon évente háromszázötvenezret végeznek, Ausztriában több mint kétmilliót – mondja dr. Magyar.

Ráadásul idehaza az orvosok egy része pillanatok alatt kimond egy végleges diagnózist, mármint hogy a beteg menthetetlen. – A leggyakrabban olyan esetekkel találkozunk, akikről vidéki kórházakban vagy más, esetleg kisebb intéz-



NÉPSZABADSÁG

Kun's article, which originally appeared under the heading *No Taxol*, alerted the public to the fact that, as a cancer patient, your survival can depend on where you are treated – and that in turn can depend on who you know or how much 'gratitude money' you pay

condition and had continuous need for tapping of ascites, I took her to my classmate who is a surgeon. He decided to operate. This is how, after two years, they discovered that my wife's tumour was operable. My wife is now feeling well, although at that time she had been told that she had only a matter of months to live."

Lawyers, specialists and representatives of patient associations come across many similar cases of patients who are not referred to a specialist centre in a timely manner. In most cases today the oncologist only sees the patient when he or she already has advanced disease.

"Ovarian surgery is done in nearly all hospitals in the country despite the fact that in theory these types of intervention are only permitted in cancer centres with good pathological services," says Dr Ágnes Ruzsa, head of the oncological department of the Zala County Hospital. "Today cancer surgery is carried out in nearly every small hospital in the country. Sometimes the patient is never referred to an oncologist. They just remove the tumour, they assume the patient is cured and send them home." According to Dr Ruzsa, who believes it should be a fundamental requirement that subsequent chemotherapy should be done only in oncology departments or centres, another common practice is that they say, "We must give something," so they give some chemotherapy, but in the wrong dose and without keeping to established protocols and prescriptions. "The important thing is to keep the patient."

Dr László Thurzó, head of the oncology clinic of Szeged, has carried out a survey of the treatments of ovarian cancer. He found that, in the given year, only 480 patients out of 1,200 had been given chemotherapy. "Only 30–35% of the patients were referred to follow-up care and were therefore treated adequately. The others disappeared from the system. This result is damning even if we take into account that the

figures include a number of older people who were in poor physical condition and therefore were not eligible for treatment," says Dr Thurzó.

Furthermore Dr Tamás Magyar, the leading oncologist of Sándor Péterfy Street Hospital, states that cancer patients' outcomes depend on where the disease is diagnosed. In some centres cancer patients can receive state-of-the-art treatment like anywhere else in the world, so this is not the primary problem. "For example, we have just removed the ovary from an eighteen year old girl. It turned out that the ovary contained a very dangerous type of cancer. The results were sent to the US for consultation, and she received the most appropriate therapy. Today she has recovered. If this had happened in a small hospital without an oncology background, this girl would not be alive today."

According to Dr Magyar, only 40% of the available diagnostic instruments are used to diagnose cancer. "For instance, in the case of pelvic cancers, MRI scanning is obligatory in order to determine the most effective therapy. Nowadays, this happens in only 50% of cases, even though carrying out the scan significantly improves the chances of being cured. This is also the case with tumour marker examination. In one year only 350,000 examinations were done in Hungary, while in Austria more than 2 million examinations were undertaken," says Dr Magyar.

"Moreover in Hungary some doctors are all too quick to state that the patient is beyond hope. In most cases we see patients whom doctors in a county or smaller hospital have given up on, despite the fact that their tumour is operable and can be treated. The only option for these patients is to look for an informal route to getting back into treatment, by seeking contacts via friends and relatives. These are the ones who refuse just to sit back and wait to die."

Carelessness? Negligence? Lack of professional expertise? Fighting for patients or reputation? Experts say that all of these are to blame for the fact that 30–40% of patients do not get adequate treatment today.

According to Dr Magyar, it is inexplicable why AIDS patients must by law be referred to a specialist institute, while in the case of cancer patients there are no such requirements. Moreover, mistakes are rarely highlighted.

"The efficacy of a clinic, department or doctor is rarely monitored," says Magdolna Dank, head of the department of the Radiological and Oncology Clinic. "This means that clinics and doctors get away with prescribing incorrect doses and regimens of chemotherapy. It is not uncommon for departments that are not eligible to use chemotherapy to prescribe a completely different drug rather than refer patients to a specialist institute where he/she could get the appropriate treatment. Medicines have different prices, and the patients could be given different drugs. Most of the time a small hospital – usually for economic reasons – chooses an inappropriate treatment, but the insurance pays for this treatment anyway. There is a need to evaluate each clinic and department, to determine which cancer services they should be allowed to provide. Moves are already afoot to regulate this situation, and departments have been informed which treatments they are authorised to administer. However, so far this is not being enforced," says the specialist medical oncologist.

According to Dr Dank, the absence of specialists is causing great problems. There is a lack of specialists in medical oncology, radiation oncology, radiology and pathology. Furthermore, it is very difficult to recruit doctors to work in oncology. Without new blood, the future of oncology is uncertain. It is widely agreed that a multidisciplinary approach is required to devel-

Clinics and doctors get away with prescribing incorrect doses and regimens of chemotherapy

op the best treatment plans and that a team should consist of radiation oncologist, pathologist, medical oncologist, surgeon, and where possible a psychiatrist. However, this is very difficult to achieve in the absence of specialists.

Mr Szabolcs Ottó, the vice director of the National Oncology Institute, speaks of an epidemiological crisis, because Hungarian cancer statistics are so much worse than could be justified given the country's level of development and the age profile of its population. International data show cancer incidence at 50,000 per 10 million inhabitants, while in Hungary the figure is nearer 70,000.

Mr Ottó has been looking for answers to the question of why so many Hungarians get cancer and end up dying from their disease, and what can be done about it. Besides the most common reasons such as smoking, alcohol and poor nutritional habits, he thinks the organisation of Hungarian cancer services plays a role, as does one other important factor: the lack of an open and honest relationship between the doctor and the patient.

Statistics show that a patient who is treated in Hungary has a 10–15% lower chance (or for some types of cancer even worse) of surviving a cancer experience than those treated in western Europe. But even within the country there are differences.

According to the Hungarian Association Against Cancer, patients are sometimes told that their required treatment is either not available, or not covered by health insurance. "Every autumn and summer patients have to face the fact that the money to pay for cancer treatments has run out and therefore hospitals stop offering these treatments," says Mrs Vasváry, the leader of the Association.

Most of the supplies of cancer medicines are allocated to the National Oncology Institute, and the drugs are allocated on the recommendation of specialists. According to oncologists and insurance companies, it is not possible for a patient to be unable to get the necessary drug, but patients' experiences tell a different story. Sometimes the National Institute refuses a request from a county hospital. In this case, patients either have to wait two to three weeks or start the treatment with another, less effective medicine. Sometimes doctors stop therapy in the middle of the course of treatment because there is no more drug available.

You can come across cases like this, even though the primary duty of all oncology departments is to provide all the necessary medication, even if sometimes it means that they have to use the medication of somebody who has passed away.

Cancers are classified into four stages. In stage I nearly all patients are curable. In the second and third stage 30–50% of patients can be cured, depending on the type of cancer, and in the fourth stage almost nobody can be cured. In Hungary, nearly one quarter of the patients are diagnosed with stage IV disease.

"It is fundamental that patients with tumours will do anything to be cured," says Dr Magyar. "In my hospital it is not possible for the leader of the decision-making team, who has the power to decide where a patient is referred, to live off 'gratitude money' [bribery], because we have an oncological committee which decides on a random basis who is referred to which doctor. I have very little face-to-face contact with my patients, and in this way my decisions can be independent."

But generally the words of the doctor-lawyer Dr Judit Kismarton are true: it is definitely the 'gratitude money' and the economic situation that are to blame for the fact that most patients are referred too late to the appropriate institute. "The fact that in many hospitals the patient is not referred to an oncologist, but is simply operated 'in-house', even if the cancer has spread, without preliminary investigations or follow-up treatment, is because by referring the patient on, the hospital loses out on both the health insurance payment and the 'gratitude money'".

Last year, according to the cancer registry, 78,000 cancers were diagnosed in Hungary. If we could implement international standards we could improve our average survival figures by 10 years. In the past 25 years the number of people registered disabled because of cancer has doubled, despite the fact that the criteria for being registered disabled have been tightened.

Minimising radiotherapy in children with rhabdomyosarcoma

Alex Mathieson

US and European paediatric oncologists are finally finding common ground over which patients need potentially damaging aggressive local treatment, and which can be spared.

The gap between Europe and North America on the treatment of young children with rhabdomyosarcoma may not be as wide as readers of recent papers in the *Journal of Clinical Oncology* might have suspected.

The main paper (JCO 23:2618-28) reported on the third study of the International Society of Paediatric Oncology (SIOP) on malignant mesenchymal tumours (MMT 89), which set out to improve outcomes for children with non-metastatic rhabdomyosarcoma and reduce systematic use of local therapy such as radiotherapy. It was accompanied by an editorial commentary from the US (pp2586–87), which explained the 'philosophical differences' that exist between the continents in relation to rhabdomyosarcoma management, predominantly focusing on the greater enthusiasm for local treatment in North America.

MMT 89 lead author Michael Stevens and James Anderson, a member of the US Intergroup Rhabdomyosarcoma Study Group (IRSG) IRS-IV investigation and co-author of the JCO editorial, are two of the main 'protagonists' in this philosophical debate. Yet while both agree that some differences still exist, they actually adopt positions much nearer to one other than the rhetoric would suggest.

"We're close", says Anderson, who is chair of the Department of Preventive and Societal Medicine at the University of Nebraska Medical School. "There's been a great deal of interaction and exchange of information over the last couple of years. It's my sense that the respective therapeutic approaches are moving closer, with the Europeans becoming somewhat more aggressive with local therapy than they have been in the past with some subsets of patients, and we in the US adopting less aggressive approaches for patient groups in whom the Europeans have shown success."

Meeting of minds

Stevens, CLIC Professor of Paediatric Oncology at the University of Bristol, UK, agrees. "We're moving towards meeting in the middle," he says. "There has been a move away from a uniform rule in North America that everyone gets radiotherapy, to a slightly more selective approach. They've taken on board our demonstration that some patients can be cured with less treatment than they might normally give, and we've looked critically at our own results and have made amendments to our strategies." The principle behind the MMT studies is to limit the use of local therapy as far as possible, particularly radiotherapy. The great majority of children with rhabdomyosarcoma are very young, yet radiotherapy historically has formed an important part of their treatment, bringing with it significant long-term effects.

The MMT 89 results in relation to overall survival, however, don't compare favourably to the US IRS-IV investigation, which featured early radiotherapy for several groups of patients, including the very young. "You can't deny that the results of the IRS-IV study look somewhat better than ours," Stevens concedes. "Their results are stunningly good for tumours of the orbit, with 100% survival claimed. We have had to accept that the MMT 89 experiment didn't work in its entirety and that some of the patients we tried to treat without radiotherapy actually do need it. We've consequently made modifications to our treatment strategies by introducing radiotherapy for more children on the basis of those results.

James Anderson (US): We've halved the radiotherapy for low-risk rhabdomyosarcoma patients on the basis of data from Europe

Michael Stevens (UK): We've introduced radiotherapy for more children, because the US results were better than ours

But the fundamental of the whole debate is – can you actually cure as many children without exposing them to more treatment than is necessary?"

Stevens accepts that the price of trying to answer this question can be high. "It brings major anxiety that some children who relapse may die because they weren't treated more aggressively in the first place," he says. "And those who don't die but are salvaged will require more treatment in the end than might otherwise have been necessary."

Treating for the long term

But keeping an eye on the long-term picture is enormously important, Stevens believes. "If we are going to create a population of young people who have survived cancer in childhood, we want to minimise the consequences of their experience of the disease and its treatment in adult life," he says. "One of the great difficulties of applying this general principle is that it is something you can talk about comfortably across a population, but find more difficult to do in relation to an individual child. But I know that if I have a two-year-old with a tumour of the orbit, I will do my best to treat him without exposure to radiotherapy if I can."

The position historically taken in North America is that it doesn't matter whether the child is two or eight – the majority still get radiotherapy and will receive treatment longer than similar patients in Europe. That approach is being softened, however, as Anderson explains.

"Patients with orbital rhabdomyosarcoma are emblematic of the difference in approach," he says. "In the US, we typically use local control as part of the initial therapy in an attempt to maximise the cure rate. The SIOP approach is directed towards attempting to minimise the late effects, recognising that they will observe high recurrence but with a very high salvage rate for those patients."

But Anderson too believes that the last couple of years have seen movement from both sides towards similar approaches. "Patients with alveolar histology tumours who were treated in the most-recently closed SIOP study received radiation as part of their initial therapy as a result of comparative analyses with the US experience," he says. "That's a case where, for a subset of patients, the Europeans have moved towards a more North American approach."
And the North Americans have reciprocated, Anderson states.

"We've recently opened a study for the treatment of low-risk rhabdomyosarcoma," he explains. "Until quite recently, the standard length of therapy in the US was just short of a year. In the new study, patients with low-risk disease have had their therapy cut to 24 weeks, largely because we know from European studies that similar patients treated for a very short time – 9-16 weeks – have done quite well. Those data gave us comfort in reducing the length of therapy."

Things have moved to the point where researchers from the two continents are considering creating a combined dataset and running some collaborative comparisons.

"We've begun discussions along those lines," Anderson confirms. "We both have an extensive historical database on the experience of treating children with rhabdomyosarcoma. The IRS-IV and MMT 89 studies were conducted almost contemporaneously, so the idea is that by assembling data from those studies in one place with variables defined in the same way, we can begin to make some formal comparisons."

While North America and Europe may be at loggerheads in some spheres, this looks to be one area where peace has broken out.

Could COX-2s stage a comeback in cancer?

Janet Fricker

Hopes for a drug that could inhibit colorectal cancer took a knock last year due to revelations of serious side-effects. But a combination therapy may now offer a way forward.

A lifeline has been offered to the controversial cyclooxygenase-2 (COX-2) inhibitors that has the potential to salvage their use in colon cancer prevention. A late breakthrough session abstract (LB-4), presented at the 96th meeting of the American Association for Cancer Research (April 16–20) held in Anaheim, California, showed the combination of low doses of the non-steroidal anti-inflammatory drug Celebrex (celecoxib) and the cholesterol-lowering medication Lipitor (atorvastatin) inhibited 95% of tumours in rat animal models.

"When used together the drugs were most effective at doses substantially lower than when used alone," said the principal investigator Bandaru Reddy from Rutgers University, New Jersey. "This may be the most effective way to maximise the anti-cancer effects of the drugs, while also minimising toxicity or harmful side-effects."

COX-2 inhibitors – widely used as anti-inflammatory and pain-relief agents – have more recently shown promise in human trials and experimental animal models as chemopreventive agents against colon cancer. It is thought they exert their beneficial effects by targeting the COX-2 inflammation pathway leading to a reduction of eicosanoid production, which in turn influences cell proliferation, apoptosis and tumour growth. In addition, eicosanoids coordinate signalling between the cell origin (autocrine) and neighbouring cells (paracrine) by binding to transmembrane G-protein-coupled receptors. It is estimated that the COX-2 enzyme is overexpressed in 71–85% of colorectal cancers.

However, such potential applications have been brought into question by recent studies suggesting COX-2 inhibitors show cardiovascular toxicity. The first indication anything was amiss came with the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, published in November 2000 in the *New England Journal of Medicine* (343:1520–28). While demonstrating a reduced incidence of gastrointestinal lesions in the arm taking the COX-2 inhibitor Vioxx (rofecoxib), the study also showed a higher incidence of myocardial infarction for this group compared to those taking the standard dose of the non-steroidal anti-inflammatory drug Naproxen (1000 mg a day). As this study lacked a placebo group, it was unclear whether the effect was due to an increased cardiovascular risk with Vioxx, or the protective effect of Naproxen, or whether it was merely a chance finding.

Two studies published in the March 17, 2005 issue of the *New England Journal of Medicine*, reviewing the cardiovascular effects of two COX-2 inhibitors have helped clarify the situation.

In the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, by Robert Bresalier and colleagues from the Anderson Cancer Center, University of Texas (NEJM 352:1092–1102), 2,586 patients with a history of colo-rectal adenomas underwent randomisation to receive 25 mg Vioxx daily or placebo. The results showed that a total of 46 patients in the rofecoxib group had a confirmed thrombotic event during 3,059 patient-years of follow-up (1.5 events per 100 patient-years) as compared with 26 patients in the placebo group during 3,327 patient-years of follow-up (0.78 events per 100 patient-years).

In the Adenoma Prevention with Celecoxib (APC) study, by Scott Solomon and colleagues from Harvard Medical School, Boston (NEJM 352:1071–80), 2,035 patients with a history of colorectal

Bandaru Reddy: Extrapolating to humans, celecoxib used in combination inhibits cancer at one sixth the dose of previous studies

Andrea Decensi: It's plausible that the lower doses may pose less of a cardiovascular risk, but further studies will be needed

neoplasia were enrolled in a trial comparing two doses of celecoxib (200 mg or 400 mg twice daily) with placebo for the prevention of colorectal cancer. Results showed that the composite cardiovascular end point of death from cardiovascular causes (myocardial infarction, stroke or heart failure) was reached in 7 out of 679 patients in the placebo group (1%); 16 out of 685 patients receiving 200 mg celeboxib twice daily (2.3%) and 23 out of 671 patients receiving 400 mg celecoxib twice daily (3.4%). "Since both these studies are in the preventative setting, the clinical implication is that the risks may outweigh any benefits," commented Andrea Decensi, of the division of chemoprevention at the European Institute of Oncology, Milan.

In the latest study, Reddy and colleagues decided to test their hypothesis that the combination of more than one drug targeting more than one gene used at very low doses would synergistically increase the cancer prevention efficacy, while at the same time lessening toxicity.

"In addition to COX-2 inhibitors we decided to focus on statins, since observational studies have shown that colon cancer rates are suppressed in patients taking these drugs," said Reddy.

He explained that by reducing levels of cholesterol, statins also act to inhibit the synthesis of bile acids, which are modified by bacteria in the colon into secondary bile acids, which include two strong tumour promoters. In addition, statins also inhibit the production of isoprenoids including geranyl pyrophosphate and geranylgeranyl pyrophosphate, which can activate some oncogenes, such as RAS. Statins may also enhance apoptosis.

In Reddy's study, rats at the age of seven weeks were given injections of the colon cancer tumour promoter azoxymethane (AOM) for two weeks, and then randomised to four groups. The first received 600 parts-per-million (ppm) celecoxib, the second 150 ppm Lipitor, the third 300 ppm celecoxib added to 100 ppm Lipitor, while the fourth group acted as a control. Results showed that, by itself, celecoxib at 600 ppm reduced the incidence, as well as the number of colon adenocarcinoma, by 80%; Lipitor alone, at 150 ppm, reduced tumour incidence by 31–41%, while the combination of 300 ppm celecoxib and 100 ppm Lipitor reduced invasive and non-invasive adenocarcinomas by 95%.

"If you extrapolate this to the human situation, we're using celecoxib at the equivalent of 120 mg/day, compared to 800 mg/day in the NEJM studies. It shows that we can get really effective cancer inhibition by using approximately one sixth of the dose," said Reddy.

Decensi commented: "It's plausible that these lower doses may not have so many adverse cardiovascular effects, but confirmation studies will need to be performed before we can take these observations further in a clinical setting."

"We decided to focus on statins, since colon cancer rates are suppressed in patients taking these drugs"

When alternative becomes mainstream

Pat Healy

Evidence base or no evidence base, complementary and alternative medicine use in Europe is edging closer to the rates reported in the US. Can Europe's doctors learn anything from their American colleagues about how to respond?

More than one third of Europe's cancer patients are using some form of complementary or alternative medicine (CAM), yet fewer than one in five of these patients have received advice from their doctor about the therapy they use, with the vast majority acting on the basis of information from friends and family. These are among the key findings of the first Europe-wide study into CAM use specifically in cancer patients, which was published this February in the *Annals of Oncology* (16: 655–663).

Fourteen countries participated in the survey, covering a total of 956 patients. In most countries, usage was around 30–40%. Two of the highest rates were reported in Switzerland (48.6%) and the Czech Republic (58.8%), consistent with previously documented high levels of CAM use in neighbouring Germany, which was not included in the study. The highest use of all was recorded for Italy, at 73.1%, but as the authors point out, the results may be skewed because the data came from a palliative care unit. At the opposite end of the scale, only 14.8% of patients in Greece reported using CAM. The authors speculate that a combination of lack of availability, high compliance with traditional medicines, cultural norms and underreporting for fear of being 'found out' by their doctors may partly explain why this figure is so low.

Though CAM use in Europe still has some way to go to catch up with the US, where rates well above 40% are consistently reported, a comparison with earlier studies shows that European patients are turning to CAM in increasing numbers – indeed CAM is now Europe's second fastest growing industry.

The term CAM covers a wide variety of therapies. The most popular forms of CAM reported in the survey are herbal medicines and remedies, with homeopathy, vitamins and minerals, medicinal teas, spiritual therapies and relaxation techniques also widely used. A particularly significant finding is that most patients using CAM were taking biologically based therapies (as classified by the US National Center for Complementary and Alternative Medicine), and that the use of herbal medicines tripled after a cancer diagnosis. Interestingly, the type of herbs used varies considerably by country: mistletoe in Switzerland, olive leaf paste in

Nazira Visram, a volunteer with the UK patient and carer group Cancer Voices, believes a change of attitudes is needed so that patients can feel able to talk to their doctors about any CAMs they use

Greece, nettle leaves/tea in Turkey, aloe vera in Serbia and Spain, Ovosan in the Czech Republic. Also reported were green tea, essiac tincture, Chinese herbs, sage tablets, Echinacea, cod liver oil, fresh juice and vegetables, vitamin E, glucosamine, chamomile, peppermint, selenium, yeast extract, multi-vitamins, Ayurveda herbs, vitamin C, soya drinks, dry thyme, ginseng, mulberry molasses, shark cartilage, fish oil, gingko biloba, milk thistle, minerals (zinc, calcium, magnesium), papaya tea, beet and carrot juice, a mixture of aloe, honey, rhaki and wine, and angelica herb.

The survey notes that improvements in physical and psychosocial well-being and increasing hope are the main reason for patients turning to CAM. But it also finds that "dissatisfaction with some aspects of conventional health care, poor doctor-patient relationship, accessibility, perceived effectiveness and desperation may also be key motivating factors." So it is not surprising that patients are turning to CAM on the word of family and friends or the media rather than information and advice offered by physicians and nurses.

Some of these patients spend a lot of money on CAM – 123 euros on average, with the highest reported amount being 4,140 euros a month. But more than half of all patients spend nothing, because they use herbs that come free.

Like many cancer patients, Nazira Visram, from Cancer Voices in the UK, is willing to try anything to improve her quality of life. But she is careful to do so only in consultation with her physicians. She has lived with a breast cancer diagnosis for three years. Her conventional treatment was a lumpectomy, followed by six weeks of radiotherapy and then tamoxifen. But her reaction to the drug was so severe that she stopped taking it after 6 months.

Pain and panic control

Nazira was experiencing severe pain and found immediate help when she started using reflexology. She describes it as "absolutely amazing", helping with pain control and calming her enough to give her time to reflect and "to get out of panic mode." She also tried yoga, which taught her to breathe correctly, which has become part of her normal routine. She says: "There is a lot to cancer. The psychological part is not understood. You are taken care of clinically, but then you need signposting throughout the cancer journey."

Her own conventional treatment carries a possible side-effect of a greater risk of osteoporosis. She takes prescribed calcium tablets to reduce the risk and has cut back on dairy products. She drinks soya milk and takes evening primrose, magnesium and zinc, "things I think will help me get a balance into my body." She has told both her oncologist and general practitioner (GP) about her use of CAM because she feels it is important to keep her doctors on her side. She also has asthma, and acknowledges that "I need their support if I run into difficulties."

Nazira volunteers as an educator and trainer for Cancer Voices, an umbrella group of

Roger Wilson, cancer patient and now director of Sarcoma UK, says patients are entitled to make up their own minds – hopefully in an informed way

patients' and carers' organisations, in the hope of improving communications between users and health professionals. This has brought her into contact with other cancer patients, so she is aware of people who want to try out things that have worked for others, without discussing it with their doctors. "Cancer is individual and your treatment is planned for you taking all personal factors into account. What works for one person won't necessarily work for another. It is this lack of knowledge that worries me." She thinks some patients fear that discussing CAM use with their doctors may affect their future treatment, underlining the need for better communications. Nazira wants action to change attitudes so that patients feel able to tell their doctors about anything they introduce into their life style.

Bradley Pearl, a GP working in a UK practice serving a multi-cultural population, has a relaxed attitude to certain CAM. He sometimes recommends homeopathy, because it uses vanishingly small amounts of substances, although he admits "one never knows what is actually in it."

His initial response to a cancer patient asking about a herbal remedy they have read about would be to find out exactly what the treatment is. Just because something is herbal doesn't mean it is harmless, he says, and there is evidence of some herbs interacting with a range of prescribed medicines.

He observes: "People are often happier taking something that is called 'herbal' rather than a prescription medicine, even though we know exactly what is in it. Herbal medicines can contain anything – and most active things we know are plant derived."

Pearl says that alternative therapies are potentially a mine field, so it is important that people using them should let their doctors know.

No evidence base

Why do some doctors take a more conservative view? "As doctors we are interested in treating people through evidence-based practice. We want to know what is there, what has been shown to work and what has been shown to be less beneficial. Not many alternative medicines have passed the gold standard of being properly investigated through clinical trials," he says. And he points out that cancer patients are a particularly vulnerable group of people who "are often grasping at straws and particularly open to charlatan practitioners."

COMPLEMENTARY OR ALTERNATIVE?

- Complementary medicine is used together with conventional medicine. An example is using aromatherapy to help lessen a patient's discomfort following surgery.
- Alternative medicine is used in place of conventional medicine. An example is using a special diet to treat cancer instead of undergoing surgery, radiation, or chemotherapy that has been recommended by a conventional doctor.

Source: US National Center for Complementary and Alternative Medicine, National Institutes of Health, USA

Most studies show that it is younger, better-educated and more affluent people who use CAM. Even the most highly qualified people can take risks when they become patients themselves.

Helle Viola Hangaard, a Danish GP, was diagnosed with breast cancer in 1998. She had been aware of a lump in her breast long before her diagnosis. When a mammogram confirmed she had cancer, she had a mastectomy followed by chemo- and radiotherapy.

She admits taking vitamins and antioxidants after another patient recommended them. The key motivation for trying these therapies was that it was something active she could do by herself. "Having cancer turned my world upside down and I knew I had to change something. My marriage, my children and my job were all OK, so it had to be something else," she says.

She did not discuss it with her own GP, arguing that as a qualified doctor herself, she was well equipped to make her own decisions. But she stopped taking the antioxidants after discovering that they can reduce the effectiveness of radiotherapy. Subsequently she also gave up the vitamins. She says she was taking up to 11 vitamin pills a day and stopped "because I was feeling so good."

Asked if she gets cross with her own patients if they don't comply with her advice, Helle stalls and says she works with patients with learning difficulties. But she admits that she does get cross with the patients' carers if they supply alternative medicines.

Roger Wilson, director of the charity Sarcoma UK, finished his conventional treatment in September 2000 when, unknown to him, his doctor believed he had only a year left to live. He does not approve of alternative therapies but supports a complementary approach "which recognises that no doctor knows everything and that patients are entitled to make up their own minds – hopefully in an informed and logical way which feels right for them."

He takes a lot of supplements and usually discusses his use with his oncologist, except when he decided to use resveratrol. "This is the active good bit in red wine, and as he had endorsed red wine, it seemed unnecessary."

Roger takes selenium, a natural trace mineral which has been lost to the western diet and may destroy cancer cells. He also takes vitaflavan and Vitamin E, both antioxidants, and beta-carotene which converts to Vitamin A in the body and is believed to inhibit tumour formation. He also takes zinc, starflower oil and folic acid.

Before taking these supplements, he was already taking multivitamins and Omega 3 fish oil. He drinks a lot of green tea and eats a diet based on organic vegetables, fresh bread, and fish rather than meat. And everything new is

CAM USE BY COUNTRY

Belgium	40%
Czech Republic	58.8%
Denmark	36%
England	29.4%
Greece	14.8%
Iceland	30.2%
Israel	32.4%
Italy	73.1%
Scotland	29%
Serbia	32%
Spain	29.8%
Sweden	30.5%
Switzerland	48.6%
Turkey	37%

Source: Use of complementary and alternative medicine in cancer patients: a European Survey. Annals of Oncology *16: 655-663, 2005. Reprinted with permission from ESMO*

The motivation for trying these therapies was that it was something active she could do by herself

TYPES OF CAM USED IN EUROPE

Alternative medical systems:
- homeopathy
- acupuncture
- Ayurveda
- naturopathy

Biologically based therapies/ alternative medical systems:
- herbs

Biologically based therapies:
- medicinal teas
- vitamins/minerals
- other dietary supplements
- other

Mind–body interventions:
- spiritual therapies and healing
- relaxation therapy
- visualisation

Energy therapies

Manipulative and body-based methods:
- massage

Other manipulative and body-based methods

Source: Use of complementary and alternative medicine in cancer patients: a European Survey. Annals of Oncology *16: 655-663, 2005. Reprinted with permission from ESMO*

checked to ensure that it doesn't conflict with prescribed medicines.

He explains: "I have seen patients die early as a result of believing 'snake oil' merchants (in one case a sharks fin merchant). I have also seen what it does to their loved ones and it is a despicable trade. There are cases where traditional medicine cannot help, we all know that, and doctors will admit it when they are up against the buffers.

"The snake oil merchants don't. For them it's the patient's fault if they don't live, and that I can never forgive. Forget the money issues, it is immoral. I know there are people who have survived using an alternative approach, good for them, but they are exceptions just as much as I am."

COMMUNICATION GAP

The evidence that one in three patients in Europe are using CAM – most of them biologically based CAM – raises some important issues for their doctors. Not least among them is the well-documented problem that few doctors will know which of their patients are taking what.

Oncology nurse Annie Angle says patients often won't talk to their health professionals because they are scared doctors will think they are weird and will try to talk them out of it. She says communications need to be improved to encourage patients to come forward, and forecasts that the doctors will eventually address the CAM history of patients as a routine part of taking their medical history – a procedure that is already under discussion in the US.

Karin Schmidt, a researcher in complementary medicine at the Peninsula Medical School of the Universities of Exeter and Plymouth, argues that there is also a pressing need for health professionals to inform themselves more on the CAM their patients are using. She is working on a new website which will offer condensed summaries on CAM therapies, which is due to start in September and is financed by the European Union. The hope is that this will prove a useful resource for doctors, and also provide patients with a much-needed authoritative alternative to the many very dubious sources of information currently found on the Internet.

One suggestion put forward by the authors of the recent study is that Europe should follow the example of the US, where 64% of medical schools offer courses in CAM. They point out, however, that this doesn't deal with the fundamental problem that for most CAMs, reliable evidence-based information just doesn't exist, and without such evidence, doctors' reluctance to advise on such therapies is understandable. They conclude that "the need to increase the evidence base of CAM therapies using methodologies that are appropriate and sensitive to CAM cannot be overemphasised."

The no-computer virus

Costs, compatibility and patient privacy have all been cited as reasons why patient records cannot be computerised. But the inability, and reluctance, of doctors and hospitals to use information technology more widely is killing thousands of people.

Whether or not a treating doctor has Alex's full medical record available can literally mean life or death," says Cynthia Solomon of Sonoma, California. Her son Alex, now in his 20s, grew up with hydrocephalus, a rare and life-threatening condition in which fluid accumulates in the brain and needs to be drained through special shunts. So Ms Solomon had no choice but to become a walking filing cabinet of records on allergies, pituitary-gland problems, brain scans and "every piece of paper a doctor ever wrote about Alex's case." She worried constantly. There were close calls, such as the time that Alex went on a trip and ended up, unconscious, in some distant hospital. Ms Solomon could not get his paper records to the new doctor and had to pray that Alex would not get the wrong antibiotics or be laid on his back, which might have killed him.

To Ms Solomon the information problem with health care today is so glaring that she eventually took matters into her own hands, as best she could. She took out a second mortgage, hired software programmers and developed a computer system, called FollowMe, for online medical records that any doctor can, in theory, access anywhere and anytime. FollowMe will not fix the world's health-care industry – only about 400 families now use it – but Ms Solomon has correctly identified the woeful, even scandalous, failure of the health-care industry worldwide to adopt modern information technology (IT).

The solution seems obvious: to get all the information about patients out of paper files and into electronic databases that – and this is the crucial point – can connect to one another so that any doctor can access all the information that he or she needs to help any given patient at any time in any place. In other words, the solution is not merely to use computers, but to link the systems of doctors, hospitals, laboratories, pharmacies and insurers, thus making them, in the jargon, 'interoperable'.

This may be obvious, but today it is also a very distant goal. According to David Bates, the head of general medicine at Boston's Brigham and Women's Hospital and an expert on the use of IT in health care, the industry invests only about 2% of its revenues in IT, compared with 10% for other information-intensive industries. Superficially, there are big differences between

BROOKS KRAFT / CORBIS / CONTRASTO

US President George W. Bush looks at an electronic medical record system during a visit to the Cleveland Clinic in Ohio, January 27, 2005. One estimate suggests that IT could prevent 2 million adverse drug interactions and 190,000 hospitalisations in the US every year

countries. In Britain, 98% of general practitioners have computers somewhere in their offices, and 30% claim to be 'paperless', whereas in America 95% of small practices use only pen and paper. But, says Mr Bates, this obscures the larger point, which is that even the IT systems that do exist cannot talk to those of other providers, and so are not all that useful.

It shows. People on the right side of the digital divide increasingly take for granted that they can go online to track their FedEx package, to trade shares, file taxes and renew drivers' licences, and to do almost anything else – unless, of course, it involves their own health. That information, crumpled and yellowing, is spread among any number of hanging folders at all the clinics they have ever visited, and probably long since forgotten about. The most intimate information is, in effect, locked away from its owners in a black box.

Many IT bosses find this baffling. John Chambers, the chief executive of Cisco Systems, the world's largest computer-networking company, says that health care is down there with mining as the most technophobic industry. Jeff Miller, a manager at Hewlett-Packard (HP), a large computer-maker, calls health care "one of the slowest-adopting industries", which is especially surreal because hospitals often splurge on the latest CAT-scan or MRI equipment, but are stingy with their back-office systems. It is, he says, like "Detroit putting out futuristic hydrogen cars but using paper processing and manual labour for the manufacturing."

This has perverse consequences. According to the Institute of Medicine, a non-governmental organisation in Washington, DC, preventable medical errors – from unplanned drug interactions, say – kill between 44,000 and 98,000 people each year in America alone. This makes medical snafus the eighth leading cause of death, ahead of car accidents, breast cancer and AIDS. "It's like crashing two 747s a day," says Mark Blatt, who was a family doctor for 20 years before he joined Intel, the world's largest semiconductor-maker, to manage its healthcare strategy. There should, he says, be more outrage.

OWEN FRANKEN / CORBIS / CONTRASTO

Medical records awaiting transfer onto computer. Britain, Spain and Denmark are pioneering national/regional networks for electronic patient records. Much of Europe, however, remains more like the US, where 95% of small practices use only paper and pen

Rich pickings

Improving computer systems, of course, would not eliminate all medical errors. But most researchers believe that they would reduce them dramatically. One study in America estimates that IT could prevent 2 million adverse drug interactions and 190,000 hospitalisations a year. Another study reckons that electronic ordering of drugs can reduce medication errors by 86%. By contrast, research published in March in the *Journal of the American Medical Association* warns that IT, if the software is badly designed, could actually increase errors. But almost everybody agrees that well-designed IT is essential to improving quality in health care.

The same goes for its cost, an increasing burden to ageing societies in the rich world and even in poor countries such as China. HP's Mr Miller reckons that redundancy and inefficiency account for between 25% and 40% of the $3.3 trillion the world spends on health care every year, and could be eliminated with proper IT. A study from a clinical research centre at Dartmouth College in New Hampshire reaches a similar conclusion, estimating that a third of America's $1.6 trillion in annual health-care spending (as of 2003) goes to procedures that duplicate one another or are inappropriate.

Estimating how much IT could save, after taking account of the considerable cost of applying it widely, is not easy. Writing in *Health Affairs*, an American journal, in January, Jan Walker and five colleagues (including Mr Bates) at the Centre for Information Technology Leadership in Boston concluded that a fully interoperable network of electronic health records would yield $77.8 billion a year in net benefits, or 5% of America's annual health-care spending. This includes savings from faster referrals between doctors, fewer delays in ordering tests and getting results, fewer errors in oral or hand-written reporting, fewer redundant

Health care is down there with mining as the most technophobic industry

The solution is to link the systems of doctors, hospitals, laboratories, pharmacies and insurers

tests, and automatic ordering and re-fills of drugs. It does not include, however, perhaps the biggest potential benefit: better statistics that would allow faster recognition of disease outbreaks (such as SARS or avian flu).

The key word in all such estimates is always 'interoperable', says Mr Bates, pointing to the differences between two pilot programmes in America. In one, the Californian city of Santa Barbara set up a city-wide peer-to-peer network (in which the computers of different practices and clinics can talk directly to one another). This allows doctors, say, to pull up portable-document-format (PDF) files from one another. But the information in them – text, with numbers buried in it – is 'unstructured' and so not very useful. It is the equivalent of faster faxing, and not what people mean by interoperability.

The other American pilot, located in Indianapolis and managed by the Regenstrief Institute, a non-profit medical-research organisation, comes closer. It has created a city-wide network in which physicians can, with the patient's permission, log on to a complete medical history that includes all previous care at the 11 participating hospitals. Already, the database contains 3 million patient records, 35 million radiology images, 1.5 gigabytes of diagnoses, 20 million order-entries by physicians, and so forth. The key difference is that, wherever possible, the data is entered in a structured and formatted form. Test results are in neat rows and columns and tagged in a way that every other computer can recognise and compare against other appropriate numbers. This is the sort of IT solution that not only cuts waste and errors, but also helps physicians to make better decisions.

What, then, would the ideal IT architecture of health care in future look like? It would start, says Intel's Mr Blatt, with wireless data entry by nurses and doctors. Practices and clinics would have secure 'Wi-Fi hotspots' – using a radio technology called 802.11 – and staff would walk around with small handheld devices that transmit all inputs to the database in the back office. Another source of input might be tiny radio-frequency identification (RFID) chips that are attached to patients and send basic information when they come in range of a radio field. Patients could also add inputs themselves. A firm called Health Hero, for instance, makes a cute little device called a Health Buddy that patients take home and plug into their telephone lines. A couple of times a day, it asks them basic questions or takes their heart rate, and sends the data to the doctor.

Behind the scenes, all this data would be formatted and stored according to recognised standards. Contrary to widespread concerns, this does not require a single central repository or any other particular hardware architecture. Instead, it relies on common software protocols and formats so that individual computer applications can find and talk to one another across the Internet. Most of these standards, such as XML, SOAP and WSDL, already exist and are used by many industries. Others, such as HL7, LOINC or NCPDP (spelling them out makes them sound no less obscure) are unique to the health-care industry and govern data interchange between hospitals, laboratories and pharmacies. On top of these, there need to be hacker-proof layers of authentication and password protection so that only the right people get access.

There is still some work to do to refine these technologies. In January, eight of the world's largest IT companies – Microsoft, Oracle, IBM, HP, Intel, Cisco, Accenture, and Computer Sciences – teamed up to form an 'interoperability consortium' for that very purpose. In general, however, "the technology is very, very ready," says Robert Suh, the technology boss at Accenture, a consultancy that is helping

Britain's National Health Service (NHS) and regional governments in Australia and Spain to implement electronic health records.

In fact, Britain's – or rather England's – NHS is among the pioneers worldwide. This year, it will begin rolling out a £6.2 billion ($12 billion) project in which five regions in England will form networked IT 'clusters' so that 18,000 NHS sites, including all family doctors and acute-care hospitals, can share standardised information on patients. These clusters will eventually be linked through a 'spine' (called the N3 and run by the main UK telecoms provider, BT) with huge bandwidth to create, in effect, one national network. Scheduled to be completed by 2010, the plan, like most IT projects, has had some early hiccoughs and has been greeted with cynicism by some doctors. But other countries will be looking to it as a model.

Another pioneer is Denmark, which began rolling out a similar network for the region around Copenhagen in 2001 and expects to complete it by 2007, before covering the rest of Denmark. Torben Stentoft, the boss of Hvidovre Hospital in Copenhagen and the head of the city's network, says that his main concern is the nitty-gritty of dealing with all of his legacy computers which need to be tweaked or replaced. But he feels that he has his society's full support. "Nobody is against this. Everybody is asking for it," he says. In particular, the Danes find nothing terribly controversial in the idea of a national health identification number, which they already have, and spend little time worrying about how to fund the new systems, since their tax kroner are doing that.

American exceptionalism

Mr Stentoft is in an enviable situation, especially if viewed from America, which has the world's largest and costliest health-care system. America is as enthusiastic as any country about electronic health records. President George Bush has embraced the idea, and he spoke about it publicly some 50 times last year. He has even appointed a "national co-ordinator for health information technology" to create a fully interoperable, nationwide network within ten years. But America's health-care system is so different from others that it faces some special complications.

The first big difference is that, whereas most other rich countries have 'single-payer' (i.e. government-run) health-care systems, America has a highly fragmented industry with many private providers and insurers doing business alongside large government programmes (such as Medicare, for old people). This means that in funding a new IT infrastructure "the financial incentives are not exactly aligned," says Mr Bates. In single-payer systems, the expenditures come out of the same pocket – the taxpayer's – that the savings go into. But in America, he estimates, the practices and hospitals that pay for the IT only get 11% of the cost savings, with the rest going to insurers and employers (who buy the insurance). The resulting mismatched incentives, says Mr Bates, could derail the entire project: "It's a situation where America could end up far behind."

This calls for some combination of government subsidies and private-sector financial incentives, argues the Markle Foundation, a charity in New York that is dedicated to the proper use of IT in health care and national security. Over half of all doctors in America work in small practices. And, say Markle's researchers, a typical practice (defined as five doctors handling 4,000 patient-visits a year) would make losses if it had to pay the estimated $15,000 a year for three years that it costs to install an interoperable IT system and to learn how to use it.

The practices, Markle concludes, therefore need incentives of $3 to $6 per patient-visit, or $12,000 to $24,000 a year, which comes to $7 billion to $14 billion a year for three years, or between 1.2% and 2.4% of total ambulatory-care revenues. The trickier question is how to administer this largesse, whether it is provided by insurers and employers or the government. The money could be disbursed directly and specifically for the IT systems. Or it could be given indirectly in some sort of pay-for-performance arrangement.

The other big difference between America and countries such as Denmark is public perception of the robustness of privacy laws. The

Opinion polls in Europe show huge support for properly regulated interoperable medical databases

European Union has stricter privacy laws than America, and Europeans have relatively more confidence in them. For information sharing, "ours is a much more porous environment," says Alan Westin, a professor at Columbia University who has written several books on privacy issues. This is not primarily an IT issue, although the Internet does seem to raise the stakes.

In February, one database broker, ChoicePoint, had to inform some 140,000 people that it had accidentally sold sensitive information about them. Also in February, a statistician of the health department in Palm Beach County, Florida, inadvertently e-mailed a list of more than 6,000 HIV carriers to all employees of the department.

This makes many Americans suspicious of plans that involve sharing sensitive health information. Although opinion polls in Europe show overwhelming support for interoperable medical databases as long as these are properly regulated, a February poll by Harris Interactive found that Americans are currently evenly split, with 48% saying that the benefits outweigh the privacy risks, and 47% saying the opposite. Some 70% of Americans in the poll worried that sensitive data (on sexually transmitted diseases, say) might leak.

This is unfortunate, says Michael Callahan, a health-care lawyer at Katten Muchin Zavis Rosenman, a law firm in Chicago, since a weighty tome of legislation was passed in 1996 precisely to prevent such leaks. Called HIPAA (short for "Health Insurance Portability and Accountability Act"), the law defines strict codes for sharing medical data and takes effect in stages. HIPAA creates a national 'floor', says Mr Callahan, with some states following even stricter statutes, and involves the federal government in enforcement and prosecution. HIPAA is not quite as strong as equivalent laws in Europe, he thinks, but strong enough.

Mr Westin disagrees. The HIPAA rules are "not at all adequate" for shared medical records, he says. So the only way to sell such records to the American public, he says, is to design the whole system with privacy as a priority. This rules out any form of medical identification card, to which Americans would be hostile (even though they think little of giving their social-security numbers, a de facto ID, when renting DVDs). It also means avoiding a central database that could be hacked. The best approach, says Mr Westin, is to emulate the 'locators' used by American police. Cops in California who arrest a New Yorker cannot access information about that person directly, but can view a directory of such information and request it from the authorities in New York. Finally, rather than allowing sceptics to opt out of the new system, says Mr Westin, the system should from the start require patients actively to opt in.

As the Markle Foundation puts it, the technology must be designed in such a way that "decisions about linking and sharing are made at the edges of the network" by patients in consultation with their doctors, and never inside the network. This goes to the very heart of the matter. For even though it is fine to start hoping for the day when interoperable electronic health records create vast pools of medical information that could be used to find new cures and battle epidemics in real time, their ultimate purpose is to make one simple and shockingly overdue change: to enable individuals, at last, to have access to, and possession of, information about their own health.

The grief that cannot speak its name

➜ Raphaël Brenner

The loss of a sibling can lead to endless suffering when the loss is not given the attention it requires and when grief work is incomplete. A courageous victim of sibling loss tells how she healed her wound and re-appropriated her personal story.

When she was 14, Elizabeth DeVita-Raeburn's elder and only brother, Ted, died of aplastic anaemia after having spent eight years in isolation.

At the funeral, a woman took her by the arm and whispered: "You will have to be very good now, your parents are going through a lot." The words made her feel "selfish, ashamed", writes Elizabeth DeVita-Raeburn as she recalls the *omertà* (law of silence) that was imposed on her following her brother's death. "My brother's illness, his death…became a frozen lake somewhere deep inside me, one that would take me years to locate, to recognize, and ultimately, to thaw."

While her parents struggled to cope with the tragedy by evasion or immersion in work, Elizabeth sank in a pattern of self-destruction, and found herself falling apart at age 26, with no idea why. She entered therapy and her book recounts the journey she undertook to reclaim her disfranchised grief, re-form her identity, and finally summon the courage to talk to her parents about her brother's death, almost 30 years after the event. A journalist by profession, DeVita-Raeburn drew on the experiences of some 200 victims of sibling loss to convey in her book the powerful emotions involved in the loss of a brother or sister.

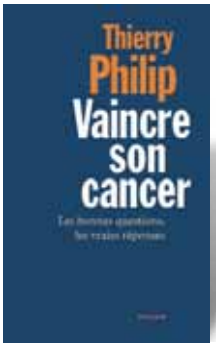
In order to heal herself, she needed first to mourn and make sense of her loss. She tells how she had to "excavate the grief" she had buried, and reclaim her story. "I found this process of narration, of telling with a point of view, healing beyond all expectation."

The Empty Room: Surviving the Loss of a Brother or Sister at any Age
Elizabeth DeVita-Raeburn,
Scribner, 230 pp, $23.00

Elizabeth DeVita-Raeburn gave herself permission to speak, a permission that had been denied to her for many years. She argues convincingly that sibling loss has been much neglected, not only at the familial level (overshadowed by parents' loss of their child, the sibling is not considered among the truly bereft), but also at the societal level (at least north American), with research on sibling loss still scant.

DeVita-Raeburn vividly evokes the process of retrieval and re-appropriation she underwent, but her psychological analysis of sibling loss is less profound and ignores important works such as those of Jacques Lacan, Melanie Klein, Nicolas Abraham and Maria Török. The amazing power of sibling relationships could also have been further explored. Finally, a metaphysical or religious approach to this topic (the death of a sibling is viewed on the same level as the death of a parent or child in Judaism) would have been of great interest, but this is perhaps the material of another book.

While most victims of sibling loss choose not to talk of their loss, DeVita-Raeburn opted for the more painful route – she opened the wound and found the words to express her suffering and make meaning out of her family's tragedy. In doing so, she healed herself. "Now I have a story and it's mine" she writes at the end of her book.



Vaincre son cancer
Les bonnes questions, les vraies réponses
Thierry Philip
Milan, 406 pp, euro 22.50

Cancer: Toutes les réponses à vos questions
Philippe Jeanteur
John Libbey
Eurotext, 240 pp, euro 19.00

"Public opinion surveys as well as the experience of physicians show there is great ignorance regarding cancer… The ignorance is as great as the anxiety it helps to sustain," writes Axel Kahn in the preface to Jeanteur's book. Structured in the form of questions and answers – What is a PET-CT? Is cancer hereditary? – Jeanteur's book provides a wealth of information, including practical tips such as relevant websites, on every aspect of cancer.

Containing no less information,

Thierry Philip's book consists of short chapters on the different aspects of cancer, from diagnosis to treatment. Philip interweaves his own experience as an oncologist with descriptions of patient cases. Although at times a little pompous, Philip acknowledges his own doubts and laments the fact that oncologists remain unaware of certain aspects of the disease, unless they themselves have sat on the other side of the table. What is most important, he stresses, is "to listen to the patient and see him as a whole person." One must hope that the human qualities evoked by Philip will help make the reality of oncology departments more amenable to patients.

Evidence-based Cancer Prevention: Strategies for NGOs
A UICC Handbook for Europe
Published in collaboration with the French and Swiss Leagues Against Cancer
UICC, 224 pp, euro 20.00

IT is a known fact that by making the appropriate lifestyle choices, up to half of all cancers can be prevented. The challenge of reducing the cancer burden lies in the ability to transform this knowledge into behavioural and societal change. Full of detailed data, useful tables and diagrams, this handbook, published by the Union Internationale Contre le Cancer, offers a wide range of evidence-based cancer prevention strategies which European NGOs can adapt to the specific needs of their countries. Part I describes Europe's cancer burden, with a highly readable chapter by Elsebeth Lynge on the social inequalities of cancer, and the various approaches (cognitive, contextual, etc.) for changing health behaviour. Part II is devoted to specific prevention strategies (tobacco control, diet, occupational exposures, screening, etc.), whose implementation, it is hoped, will bring about real change. Finally, the book (available also in French, German and Italian) provides recommendations for comprehensive cancer prevention programmes.

Copies can be ordered from the UICC (fax +41 22 809 1810).

Martindale: The Complete Drug Reference
34th edition
Edited by Sean C. Sweetman
Pharmaceutical Press, 2766 pp, £275.00

First published in 1933 by the Royal Pharmaceutical Society of Great Britain (a financially independent organisation), *Martindale* provides comprehensive information on drugs

and medicines. Thoroughly updated and expanded, the 34th edition is divided into three parts. By far the largest, Part I contains 4418 monographs on drugs (including drugs still under evaluation) and ancillary substances arranged in 51 chapters according to their therapeutic uses and actions. Each chapter begins with a short but thorough disease treatment review followed by a description of each drug. These are presented in alphabetical order according to the chemical names and in a standard format: nomenclature, pharmaceutical information, adverse effects, precautions (including contra-indications), pharmacokinetics, uses and administration, name of proprietary preparations according to country. The texts are written in a remarkably concise, clear and balanced style. As an example, in the chapter devoted to antineoplastic drugs (102 pages), the disease treatment review addresses adverse effects and their treatment, precautions, interactions, resistance, choice of antineoplastics (with a very useful table of common chemotherapy regimens for malignant diseases) and 21 pages on the management of malignant diseases.

Part II consists of a series of 926 monographs on not easily classified drugs and other substances, herbals, and drugs no longer clinically used but still of interest.

Part III (630 pages) contains brief details on proprietary preparations from 32 countries (all Western countries plus others such as India, Argentina, Chile, Brazil, Thailand, etc.) and covers drugs supplied on prescription as well as those sold directly to the public.

Beyond its encyclopaedic dimension – no other work compares in breadth and depth of coverage – *Martindale* is unique in its field for other reasons. The book provides healthcare professionals with unbiased, evaluated information on drugs used throughout the world and it is based on a huge number of sources from scientific and medical literature, including major studies, guidelines, and useful reviews. Information from pharmaceutical companies is also used, but only in conjunction with other available data.

The bibliographical references (more than 37,500) appear at the end of each paragraph and cross-references to the disease treatment reviews also appear in the drug monographs.

Despite its size, *Martindale* is easy to handle thanks to its comprehensive general index (314 pages!). Entries refer to drugs (by monograph title, other approved names, synonyms and chemical names), diseases and proprietary preparations. There is also a directory of manufacturers containing some 9,500 entries for all the products and proprietary medicines mentioned in *Martindale*.

The numerous headings, together with the new typography and layout, make this 34th edition very readable.

Its uses are multiple: it enables physicians to verify specific points, it deepens their knowledge of drugs and their role in therapeutical strategies, and provides updates on ways of handling pathologies. The copious bibliographical references are also of great use both to physicians working in hospitals and those in general practice.

Reliable, comprehensive and impeccably organised, this book (also available in Spanish) is still the ultimate reference in therapeutics.

More up-to-date information from *Martindale* can be obtained from various electronic versions (www.medicinescomplete.com).

Manual práctico de hematología clínica
2nd edition
Edited by Miguel A. Sanz and Enric Carreras
Antares, 304 pp, euro 32.00

IF handbooks are intended to be highly accessible, both in shape and content, then this pocket-sized handbook of clinical haematology is an ideal companion for internists, hospitalists and family practitioners involved with haematology and particularly with malignant haemopathies.

Since it was first published three years ago, the book has been updated and revised and covers the core knowledge of haematological disorders.

Its originality lies in a clever format consisting solely of highly useful tables, informative diagnostic and therapeutic charts and algorithms. Each pathology is presented in the same format, covering epidemiology, clinical aspects, diagnostic tools, staging, prognostic features, treatment, etc.

The succinct yet detailed presentations (including a small chapter on lymphoproliferative diseases of granular lymphocytes) provide readers with a quick view of each pathology and help to orientate them in the world of haematology.