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Ulrik Ringborg

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Shameful statistics of pain

Kathy Redmond ■ EDITOR

In early March the International Narcotics Control Board (INCB), a UN agency, issued its annual report highlighting – yet again – the plight of millions of people around the world who continue to suffer acute and chronic pain because of insufficient use of analgesics.

How can this still be happening, nearly a quarter of a century after the World Health Organization made a concerted effort to promote pain relief with the launch of its simple strategy, the 'three-step analgesic ladder'?

It's not all bad news – global consumption of opioids has more than doubled over the past decade. However, this has occurred mainly in Europe and North America. In 2006 these two regions, which contain less than 20% of the world's population, accounted for 89% of the global consumption of morphine. Even here, the picture is far from perfect. A survey of nearly 5,000 cancer patients conducted last year in 11 European countries found that one in two patients suffer moderate to severe pain, while more than 10% of those surveyed indicated that their pain is sometimes so bad that they want to die (see www.paineurope.com). What must life be like for cancer patients in the developing world?

Inadequate knowledge and skills in pain management are partly to blame, but so are regulatory impediments and economic constraints. Irrational and entrenched fears about the risk of opioid addiction among patients and professionals alike also play a role.

Opioids such as morphine are not exorbitantly expensive and should be used, as appropriate, in all cancer patients who need them. Given all the technological and scientific advances we can draw upon, it seems barbaric that anyone should be left to live with unrelenting pain or die screaming in agony.

This is an issue of basic human rights. Governments have a moral responsibility to ensure that all their citizens can access appropriate pain control, by identifying and addressing national impediments to state-of-the-art pain management, including overly bureaucratic regulations governing the prescription of opioids.

Health professionals also have a moral responsibility to equip themselves with the knowledge and skills they need to manage pain effectively. Anything less would be a dereliction of duty.

A major effort will be required if we are to turn around the picture of pain management presented in future INCB reports. But it has to be made, to ensure that the many millions of people diagnosed with cancer in years to come aren't forced to face the excruciating and life-sapping pain that is the reality for huge numbers of cancer patients today.

Ulrik Ringborg:

tackling the fragmentation of Europe's cancer efforts

Marc Beishon

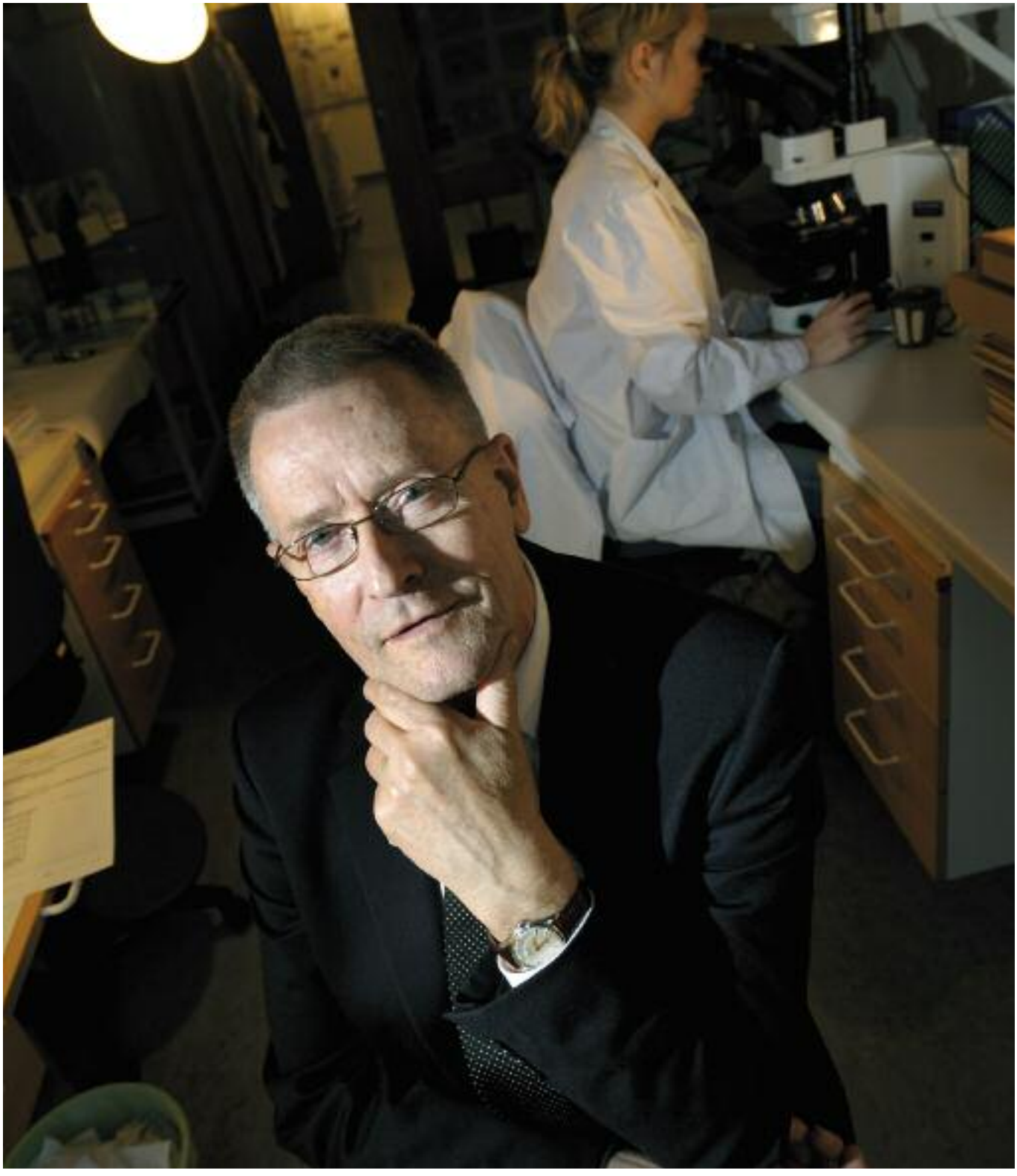
Ulrik Ringborg remembers a time before pressure on cancer services led Sweden to abandon a model that combined clinical and research responsibilities. He believes comprehensive cancer centres, similar to those in the US, are key to restoring that link, and could provide the backbone to unify efforts to improve cancer care in Europe.

The challenge of overcoming fragmentation in the European cancer effort has been a major preoccupation among key players for some time. According to Ulrik Ringborg, professor of oncology and director of the Cancer Centre Karolinska, in Stockholm, building and strengthening comprehensive cancer centres (CCCs) – where care and prevention is integrated with research and education – will be crucial to any solution, both at a national and Europe-wide level. As president of the Organization of European Cancer Institutes (OECI), he is determined to play his part, and the Karolinska gives him a very strong base from which to work.

"Cancer is very strong here. We are the only one outside of the US to make a list of the top 15 most effective cancer centres – ranking number 12 in a recent bibliometric analysis," says Ringborg. "Karolinska overall is a big organisation with some 18,000 employees, and up to a quarter of the resources and as many as 120 research groups are devoted to cancer. But we still have a great deal of fragmentation among the various clinics, which means we are not carrying out true multidisciplinary working for all patients. And are all those research groups collaborating in an optimal way? Of course not. The challenge for us – and for all university hospitals around Europe – is how to delineate a comprehensive cancer centre that includes advanced treatment and research."

Such CCCs cannot exist in isolation, he adds. Few hospitals or dedicated cancer institutes, if any, have the scale of the major American centres, and more effective translational research will not happen around Europe without collaboration both among research groups and among centres. "We need to have a common view of what translational research is," says Ringborg. "It is not just about bridging basic and clinical research, but also about structured implementation into routine care. The whole process goes from basic to outcome research – but there is an enormous gap in introducing new approaches into healthcare systems and evaluating them. We have especially to bridge the implementation gap as well as the basic–preclinical divide."

Pointing to success in rare cancers, such as



JANERIK HENRIKSSON

"It was possible then to carry out clinical duties in the morning and research later on – but that's changed"

some leukaemias, where cross-border collaboration is more or less forced on researchers and clinicians [see also Spotlight, p42], Ringborg mentions new pan-European organisational initiatives he believes will greatly increase such working. Last November, heads of many of Europe's top cancer centres and institutes met in Sweden and came up with the 'Stockholm Declaration' – a mission statement for creating a collaboration platform among the most active centres and basic/preclinical research organisations [see also Grand Round, p17].

Meanwhile, the OECI is currently piloting accreditation criteria for CCCs, not least to help expand the number in Europe – the current membership of around 60 needs to almost double, says Ringborg.

Other initiatives he flags up include the Network of Core Institutions (NOCI), a research-oriented group of élite centres under the auspices of the European Organisation for Research and Treatment of Cancer (EORTC); the TuBaFrost biobanking project led by the OECI; and the Eurocan+Plus project, funded by the European Commission (EC) to look at how the European cancer effort could be improved (Ringborg was a leader of one of the work packages).

It is, he says, an encouraging picture, and these are by no means the only promising avenues – links with the EC's Innovative Medicines Initiative and Initiative for Science in Europe are also ongoing. "We cannot put all our eggs in one basket – but we do have one message," he says.

That message emphasises the CCC as the building block for Europe, and Ringborg says his primary mission – and one that he spends at least half of his time on now – is developing true comprehensiveness at the Karolinska.

Ringborg was not earmarked for medicine at all – he was a talented pianist and seemed destined for an arts career, but felt he was being pushed too hard in this direction. "I was also interested in psychology and how the mind works, and went into medicine with an aim of doing brain research." After initial training in Gothenburg, he moved to the Karolinska Institute in the late 1960s, where he was able to combine research in cell biology (and landed a PhD on RNA synthesis on the salivary gland cells of midges), with the completion of his internal medical training.

He benefited from having a superb mentor – Jan Waldenström, one of Sweden's most famous medical scientists (who gave his name to a rare type of non-Hodgkin's lymphoma, Waldenström's macroglobulinaemia). Thus inspired, Ringborg chose to combine his basic and clinical skills in oncology, and he went on to obtain a combined Swedish qualification in medical oncology and radiotherapy.

It was an age where, at the Karolinska at least, clinicians were actively encouraged to build research careers. "The then director, Jerzy Einhorn, understood that to build oncology it is very important to involve preclinical research, and he recruited people with academic backgrounds and provided us with small labs. It was possible then to carry out clinical duties in the morning and research later on – but

ORGANIZATION OF EUROPEAN CANCER INSTITUTES

The Organization of European Cancer Institutes held its first general assembly in 1980 – some way behind its US equivalent, the Association of American Cancer Institutes, which was founded in 1959 and currently comprises 91 of the country's main academic and freestanding cancer research centres. With around 60 members, the OECI still has long way to go on the membership front, as Ringborg acknowledges. Its current primary initiative – cancer centre accreditation – should attract more interest, he says.

In addition to an accreditation team, the OECI has working groups for improving clinical guidelines, education, new technology development and pathobiology, where the main initiative is the TuBaFrost tissue bank project. TRANSFOG, a project working on the systematic identification of novel cancer genes, is also run by the OECI. Its next scientific conference and general assembly is scheduled for 20–24 May in Genoa. For further information see www.oeci-eeig.org

of course that's changed thanks to increased clinical demands and the huge increase in complexity in cancer research."

Cancer clinics also had dual clinical/academic responsibilities, which were later split up in the face of political pressure to deliver hospital services. Ringborg was among the last to enjoy such dual working, then common in Swedish university hospitals. Rebuilding the links – but in a way that accommodates modern working – is a key part of his work now at the Karolinska.

Ringborg's own work took him into several special interests, including head and neck cancers and sarcomas, but his main interest is in melanoma. He co-founded the Swedish Melanoma Study Group as far back as 1977, and this has provided a model for the type of multidisciplinary working that he feels is essential for delivering that weaker part of many cancer centres' activities: implementing innovation in day-to-day practice.

Having a multidisciplinary melanoma group in place at the Karolinska made it far easier and much faster to introduce new findings into clinical practice, says Ringborg (and Sweden has carried out important clinical melanoma trials on its own part). "I remember when studies came in showing that it was not necessary to carry out lymph node dissection in head and neck melanomas. We were able to agree that in just six months or so we would change our care programme and end all such procedures in the Stockholm area, as we were able to measure outcomes and show we were not affecting the prognosis negatively."

Another example was implementing a much smaller surgical margin around thin tumours – 1 cm instead of 5 cm – and also decreasing surgical margins on tumours of intermediate thickness. "When we'd looked at the data we could see we could change practices almost immediately," he says. "But without the right infrastructure to implement them and evaluate outcomes, it could be years before change happens, as indeed happens in many places."

A prevention programme of note was started in 1987 to identify people with a genetic predisposition for melanoma, now carried out in most parts of Sweden using a standard protocol for collecting data, held centrally at the Karolinska. Sweden also has a national melanoma care programme and registry as a result of work by the Swedish Melanoma Study Group. "With this kind of structure available to cancer centres you can have a dynamic healthcare system – but otherwise you are lost," says Ringborg. He singles out Scotland and Australia as other countries with strong groups in melanoma developing good patient registers, but says these are lacking in other countries, notably the US.

In 1992, as the health sector was starting to be hit by financial restraints, Ringborg reluctantly stepped up into management, filling the posts vacated by Jerzy Einhorn of director of the cancer centre and head of oncology at the hospital. "Sweden had been in a privileged position, but budget cuts were starting to bite then. It was my colleagues who persuaded me to apply, as I'd decided not to initially," he says.

He took up his new managerial responsibilities within a system of cancer care that had been reorganised in 1974 around oncology centres based at university hospitals – building dedicated cancer centres had been deemed too expensive. Each hospital had the mission of integrating cancer care in its region, and common care programmes were drawn up, regional registries established and screening developed.

It had proved to be a good model for evidence-based care, but the structure has been left wanting, says Ringborg, due to financial cut-backs and increasing complexity in oncology, which 'traditional organ-oriented clinical specialties' are ill-equipped to deal with. The growing numbers of chronically ill, and more elderly patients, are putting the system under further strain, he adds, with the result that the quality of service is patchy. "Inequalities exist, above all, in the management of patients with recurrent disease."

"With care programmes and registries you can have a dynamic healthcare system – otherwise you are lost"

It has been dubbed 'Karolinska Inc' on account of its commercial approach to working with industry

The lack of a national cancer plan makes it harder to address such inequalities, though plans are afoot to develop a national cancer strategy. The country does not yet have the type of networking initiatives seen in France, Italy and the UK for cancer centres and translational research, but of course it is not the only European country with such a fragmented system. It all adds to Ringborg's determination to see the Karolinska playing its part as a comprehensive cancer centre at both national and international levels.

Yet Sweden certainly does not languish near the bottom of European cancer league tables – quite the reverse. "If you look at the Eurocare data, we have some of the best figures, such as for breast cancer, as we have a good screening programme and success in treating primary disease. But all this good work can be undone if we don't have the right approach for the future."

And since government funding was curtailed, the Karolinska Institute generally has been very successful at raising funds for biomedical research – indeed it has been dubbed 'Karolinska Inc' on account of its commercial approach to working with industry and taking advantage of a Swedish rule that allows scientists to own their own discoveries. An 'innovation system' was started in 1996, and the institute is to be found among the leaders in most rankings of medical universities for research.

For cancer, Ringborg has a significant set of achievements to look back on over the 15-plus years since he took over from Einhorn – especially in research. "Without doubt the best is building the Cancer Centre Karolinska research labs next door to the Radiumhemmet [the first cancer treatment clinic in Sweden, sited on the main Karolinska campus]. I helped raise a lot of money for this building and we are celebrating its 10th anniversary this year. It is very important to have researchers close to the clinic, and it has attracted groups who have moved from elsewhere in the Karolinska campus and from other institutes." The CCK, as it is known, is an independent foundation, and its labs are at the disposal of staff at both the Karolinska Institute and the hospital.

Strong research groups include those working on tumour immunology, the P53 protein, tumour infrastructure and biomics. Almost half of the Swedish Cancer Society's funding already goes to the Karolinska, and Ringborg says little more national money can be expected – so the European Commission is another important source, and there are several international research groups coordinated by his teams.

Other highlights are the establishment of a clinical trials centre, and a rehabilitation centre for cancer patients – Ringborg reckons this is one of the few in Europe, and covers both pyschosocial and physical therapy (he mentions the Montebello Centre in Oslo as another example).

Ringborg's ideal of a CCC received a boost four years ago, when a combined Karolinska University Hospital was formed by merging Stockholm's two university hospitals – Huddinge hospital in the south of the city and the Karolinska in the north. The many groups involved in cancer are now being streamlined across the sites, organised in preclinical and basic research and in wider networks based on disease type. So far 12 networks – on tumours such as skin, lung, breast, and head and neck – have been set up, each aiming to bring together clinical research, nursing, basic research and epidemiology. The hospitals had for some time been under the control of Stockholm county council, and not the state – and it is the local politicians and the Karolinska Institute, says Ringborg, who put their weight behind not just the hospital merger but also a wider strategy to overcome the divide between the clinical and academic worlds, called the Stockholm Academic Health Care System, which has cancer as one of its core health 'profiles'.

Comprehensive means the four 'cornerstones' of prevention, care, research and education – working in such a way as to create 'innovation' – a word

JANERIK HENRIKSSON

Towards a comprehensive cancer centre. Karolinska's Radiumhemmet is the oldest cancer clinic in Sweden. Ten years ago, Ringborg oversaw the establishment of the Cancer Centre Karolinska research labs right next door

used a lot by Ringborg. "A CCC is the only place where you can have both high-quality care delivered by multidisciplinary teams and an integrated research process, from basic science to innovative outcomes for patients," he says. "But you do need a critical mass in terms of size."

It might seem that, in Stockholm, Ringborg has all the resources needed to establish a true CCC. But, as he points out, large though the Karolinska campus may be, it is relatively small compared with the giant CCCs in the US, such as MD Anderson in Houston – indeed, there are relatively few very large centres in any part of Europe, he notes. "We now have more than 200 different cancer diagnoses – the subgroups of patients is rapidly increasing and we need more patients and technical platforms such as large tissue banks to carry out advanced research."

While recognising that the US does have problems in collaborative working, partly owing to the diktats of intellectual property policy, Ringborg considers that the US National Cancer Institute has made great strides in defining the qualities of a CCC, and the sheer size of most of the centres means they are more self-sufficient in terms of infrastructure and competence. "The only way for European centres to attain the same level of comprehensiveness is to collaborate," he says – and to participate in accreditation to help ensure that common standards are practised.

The OECI's accreditation initiative is modelled on that of a registration methodology for CCCs in the US, says Ringborg and, suitably adapted, it is currently being piloted in a few European centres

Twelve networks, based on disease type, bring together clinical and basic research, nursing and epidemiology

A culture of collaboration. In 2005 Ringborg and Thomas Tursz, director of the Institut Gustave-Roussy in France, signed up to a programme for cooperation. Ringborg is now intent on widening such collaboration to encompass all of Europe's leading cancer centres

before a launch this November [see also Grand Round, p 16]. It is certainly a searching tool – comprising some 300 questions – and the aim is that all OECI members will be assessed for accreditation. "It is a methodology by the profession for the profession – to check yourself and also benchmark against other centres, and so build a structure for pan-European quality assurance," he says.

The test of comprehensiveness involves assembling the kind of multidisciplinary teams that the Karolinska has had success with, such as for melanoma. Ringborg recognises, however, that it can be difficult to unite functions that are often fragmented – particularly as the majority of centres have been carved out of university hospitals. Apart from the dominance of organ-based surgery, he refers to imaging and pathology, where cancer is only one part of their remit. "But you can only define comprehensiveness in terms of teams that provide all the functions that patients need, preferably in one place," he says. Local geography – reaching all cancer patients within the centre's region – is another challenge, and Ringborg reports that just 30% of people go to a major centre at present, taking France as an example.

He points out, however, that dedicated cancer centres, such as the European Institute of Oncology in Milan, and Jules Bordet in Brussels, do not hold all the advantages. "Increasingly, chronically ill people with cancer also suffer from other conditions that require other specialists to be available." Some dedicated centres may also lack close ties with academic researchers, he notes. Fragmentation is also exacerbated by private healthcare – Ringborg mentions Germany as a country where much medicine exists outside of the influence of public cancer centres.

The OECI is clearly the 'glue' that is working to bring together the top cancer centres, alongside the European cancer societies and research groups. And Ringborg, with others who drew up the Stockholm Declaration, has the ambition to fully realise the research side in a collaborative translational research platform that will unite the most active CCCs and also basic/preclinical research groups. "There would have been objections to this level of collaboration 10 years ago, but not now, given the challenges we face," he says.

Much debate has gone on about the divided and duplicated nature of European cancer research, and there is some talk about establishing a central European cancer institute. Ringborg and his colleagues believe that a virtual, collaborative model is the only workable solution to unite what most are agreed are particular European strengths in basic and preclinical research, at leading centres such as Heidelberg, Cambridge and Amsterdam.

The aim ties in with last year's European Union green paper, *The European Research Area: New*

Ringborg and his colleagues believe that a virtual, collaborative model is the only workable solution

"The hard part is persuading politicians we can succeed, and for that we must speak with one voice"

Perspectives, which contends that translational research is not as effective as elsewhere for all types of science. "But we have special potential to develop projects that are difficult to do elsewhere, such as pan-European biobanking, which could especially help address rare tumour types and develop more personalised medicine," he says. "We need to focus on what Europe can be good at. And the question for translational research is not that it isn't being done, but how to optimise it."

That is where the multi-pronged attack from the OECI, the Stockholm Declaration, EORTC/NOCI and the various EC initiatives come in, and Ringborg is clearly a consummate networker, with knowledge of, or presence in, nearly all the key projects. There is less money for cancer in the EU's Seventh Framework Programme, he says, but he is optimistic about the impact of Eurocan+Plus. "I have the impression the Commission is interested in a European cancer platform, and that the negative views some have had about specific funding for cancer will change."

Not surprisingly, Ringborg is also a firm supporter of the widest type of European cancer society, and finds it difficult to understand why the European Society for Medical Oncology (ESMO) chose to opt out of the new European CanCer Organisation (ECCO), on which he was a board member. As Håkan Mellstedt, the immediate past president of ESMO, is based at the Karolinska, there has been no shortage of discussions on the issue, he says.

Ringborg's key mentors go back to Jan Waldenström and Jerzy Einhorn, both no longer with us. But he is close to a number of his fellow cancer centre directors, in particular Thomas Tursz, head of Institut Gustave Roussy in Paris, and no doubt shares with him his chief frustration – local funding difficulties. He considers the controversy created by the Karolinska Institute report on the relationship between cancer drug access and outcomes in different countries to be a 'small one'. "I have no problem with the criticism of the methodology by Michel Coleman [see *Cancer World* Sept–Oct 2006], but there are differences in the uptake of drugs and some indication that the hypothesis of different survival rates is true. We cannot say more than this for now."

Apart from his organisational work, Ringborg continues with some input to melanoma research, and a little teaching, and he chairs a Swedish national advisory board on UV radiation protection. He has also co-written a recent textbook on skin cancer and a commentary on the 'forgotten' problems of non-fatal forms, such as squamous and basal cell carcinomas, which have significant management and cost issues. Cancer centres, he adds, ought to play a greater role in prevention work in society.

Ringborg has five children, all grown up now, and sounds pleased that one is preparing for a medical career. His great pastime, not surprisingly, is music – he still plays piano to high standard and listens to a lot of music. One outstanding performance he mentions was given at the last Nobel Prize ceremony by Chinese pianist Lang Lang. Ringborg is a member of the Nobel Assembly, courtesy of his position at the Karolinska, and he votes on the award for the prize for medicine and physiology, and takes part in news conferences on awards that relate to cancer, such as the 2001 prize to Leland Hartwell, Timothy Hunt and Sir Paul Nurse for work on cell division. That must be one of the most privileged 'extras' for any job in medicine.

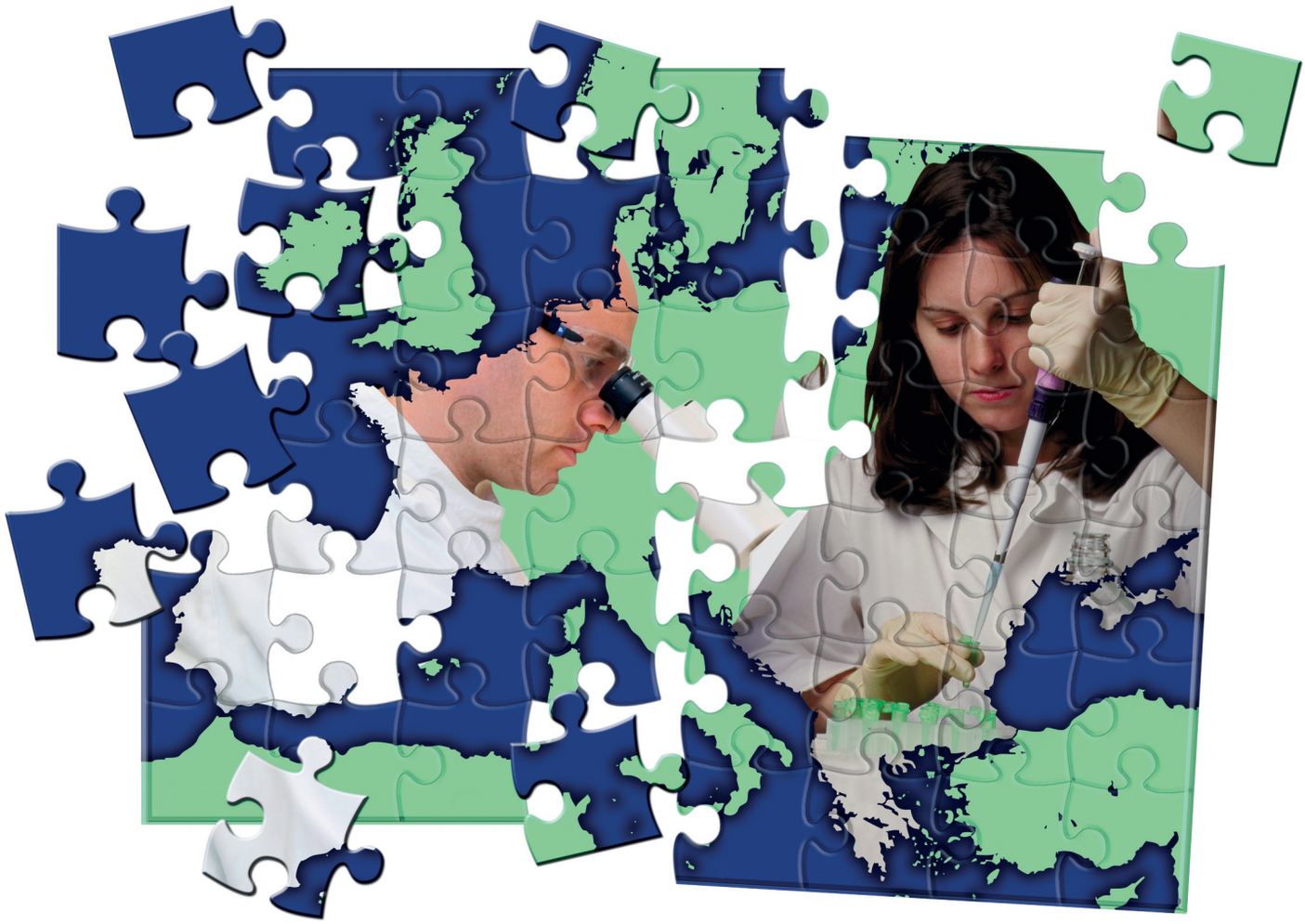
It must be especially poignant to meet the world's greatest medical scientists – many responsible for fundamental breakthroughs – and then to gauge just how far the discoveries have really made it into clinical practice. Attaining the goal of comprehensiveness will, Ringborg says, show funders a direct correlation with faster and better outcomes.

"Too many cancer professionals see the difficult part of the job in obtaining more resources – more beds, nurses, equipment and so on. These are actually the easy bits to do. The hard part is persuading the politicians we can succeed with cancer and for that the profession has to speak with one voice."

Translating good science into new treatments

Hannah Brown

Europe has money, human resources and a basic-science base that produces world-leading cancer research. Why, then, aren't these assets being translated into clinical advances?



With a list of research interests that includes several types of vaccine against the carcinogenic human papillomavirus, and a group that has produced candidate products waiting for clinical testing, Lutz Gissmann, a professor in the Division of Genome Modifications and Carcinogenesis at the German Cancer Research Centre in Heidelberg, was expecting to have no trouble translating his basic research findings into clinical developments.

But despite a firm emphasis on such translational research from his institution's management, Glissman has found organising phase I clinical tests of promising vaccine candidates far from easy. His frustration is palpable. "There is a lot of high-quality basic research in Europe, but we are missing the bridge to bring good ideas from the research lab to the clinic," he explains. "We need to run phase I clinical trials because, unless we do, we can't proceed into phase II – and big pharma will not be interested."

So if he has institutional support and good ideas, what is holding up Glissman's research? "Funding, funding, funding," he answers. "Not enough funding, and that which does come is at the wrong position." Glissman says the European Commission, the executive branch of the EU, is partly to blame for this unfortunate situation. Its excessively complicated grant application process is laden with burdensome regulations, generating a lot of hard work for scientists seeking financial support, and frequently rewarding their efforts with failure. "It's good money but it is tough to get," he says. But the main problem behind the financing gap for translational studies, claims Glissman, is that while in the US, small to medium-sized biotechnology companies take on promising product candidates at an early stage, in Europe they are reluctant to do so.

On the surface, at least, entrenched attitudes to financial risk on either side of the Atlantic seem to underlie this impasse. According to Tomas Jonsson, who works in the Enterprise Directorate of the European Commission on issues to do with biotechnology firms, companies in Europe are risk averse because it is more difficult to raise capital here, so they are less likely to invest in very early-stage products. But this, he says, is not the full story.

An October 2007 meeting at the European Medicines Agency, where pharmaceutical and biotechnology companies were invited to share their opinions on barriers to product development, drew out deeper concerns with the European research process. Rather than cultural differences being the obstacle to investment, there seems to be a more fundamental problem with cross-border research: fragmentation at almost every level of the process among EU Member States.

A heterogeneous mix of 27 nations with different research standards, equipment, infrastructure and policies, Europe is by no means a natural candidate for harmonised research efforts. And although by encouraging cross-national collaborations, the €50bn budget for science that is channelled through the central European Framework Programme (FP) has forced scientists to look outside their national borders for research partners to receive a share of EU funding, the bureaucratic and practical barriers to such work mean it rarely achieves what the Commission and the scientists had hoped.

This situation is not only professionally unsatisfying for scientists, but cancer outcomes are also lagging behind as a result. Jonsson explains: "Europe has academic excellence in pharmaceuticals and biotechnology, but there are problems trying to commercialise these. We don't necessarily need more research or the capacity to invent new biopharmaceutical drugs, but we do need to make it a bit smoother to get to the point where products can go through clinical trials and be commercialised. This requires improvements in finance, the patent system, and in collaboration between academics."

Sadly, an extension of the fragmentation problem within the EU's governing structure itself means these issues are extremely challenging to solve. Translational research cuts across the disciplines of healthcare provision and biomedical research – responsibilities that are inconveniently distributed between national governments and central European power. Politicians juggling the complex issues of national sovereignty and effective supranational government are careful not to impose too much top-down regulation on Member States wary of giving away their national flexibility in healthcare. But where science is concerned, unless there is a way to make a more coherent and less patchy research framework across the continent, it will be extremely difficult to address the fact that few, if any, cancer centres are sufficiently large to deliver multidisciplinary care and to undertake the kinds of trials that are now necessary to advance cancer research.

There is another driving factor behind the recent awareness of the need to better coordinate research across the continent: the departure of the pharmaceutical industry to more profitable and less bureaucratic shores. "Pharmaceutical companies are

Fragmentation at every level of the research process is holding back the development of new products

"We need to link centres of excellence in basic science and clinical areas to harmonise infrastructure"

moving from Europe to the USA," explains Ulrik Ringborg, a professor in oncology and pathology at the Karolinska Institute in Sweden and head of the Organisation of European Cancer Research Institutes, who is advocating for a formalised network of cancer research centres in Europe as a way to increase what he terms "critical research mass" (see also Cover Story, p4). "When we ask them why they are moving, they say they want better collaboration with academia in Europe," he adds. "Specifically, they want long-term collaborations on translational research, drug development, and personalised medicine."

So, if Europe is to continue to make significant contributions to the advancement of cancer care – and attract the necessary funding from industry – politicians and scientists alike are now realising that something has to be done to coordinate cancer research more effectively. What is more, according to Ringborg, since current trends predict that more and more clinical trials will focus on increasingly selected patient groups, requiring large multinational collaborations and the coordinated funding to support them, there is an urgent need for some common ground rules on standards for data collection, tissue storage, and sampling. But what form this coordination should take is far from clear. The problem is, while all stakeholders are at last in agreement over the scale of the problem fragmentation poses, there has not yet been a successful effort to implement solutions. Though not for want of trying.

Defining the problem

Efforts to tackle the fragmentation issue in cancer research first found a high-level champion in 2001 when European Enterprise Commissioner Philippe Busquin brought together European cancer research managers and top cancer researchers in a meeting aimed at bridging the research performance gap between the US and the EU. As a result of these discussions, the European Cancer Research Managers Forum was set up to create "a European vision regarding cancer care and research." It is currently headed by Richard Sullivan, a professor at the London School of Economics, and formerly Director of Clinical Programmes at Cancer Research UK.

Part of the organisation's work has been a series of ongoing studies focusing on defining a set of criteria for what constitutes a 'comprehensive cancer research centre' – a research institution of sufficient size and diversity to deliver multidisciplinary care to a large patient population and bring together basic scientists and clinicians in the quest to advance new treatments through clinical testing. According to Sullivan, while there are several such centres dotted across the EU, the lack of classification criteria means other centres are not necessarily aspiring to the accolade, so innovation is somewhat stalled. Creating a labelling system, he reasons, would generate a methodology to improve the centres in Europe.

Underlying the proposed accreditation system is the rationale that the main function of comprehensive cancer centres is innovation. Ringborg is also an advocate of the power of recognising the unique situation of these institutions: "In order to be innovative you need cancer care of very high quality along with integration with research," he says. An accreditation system developed by the Organisation of European Cancer Institutes, which he heads, is now in the final phase of testing. "We will soon have methodology available for analysing and benchmarking the centres," he says. The hope is that the act of benchmarking centres as higher quality will create harmonisation and stimulate collaboration.

But this plan is fraught with difficulties. There is a lot of disagreement over what constitutes a cancer centre. "We have a kind of mix and match approach," says Sullivan of the current system of classifications. And he cautions that a comprehensive cancer centre 'club' is only a useful concept if it solves some of the other problems in cancer research – specifically funding. "It has got to have a raison d'être," he says, "otherwise it is a waste of time. If it is about lobbying for money from the Commission and getting money into trans-European research projects, then fine, but otherwise not. You don't want researchers focusing on accreditation, you want them to do the research."

There is further doubt – including from Glissman – over whether such a classification system will actually add anything to the numerous well-run and large centres performing this function already. However, according to Ringborg, such administrative discussions are an important precursor to solving another of Europe's key fragmentation-related issues: lack of critical mass. He has been strongly advocating for a formalised comprehensive cancer centre network for several years, because he believes it is a necessary step to reflect the changing climate in cancer research. "If you go 10 years back in time, many people in cancer centres thought that their institution was good enough,

big enough, and that they could do research well enough. But that has changed," he says.

"We now need to link centres of excellence in basic science and clinical areas in order to harmonise infrastructure: biobanks, patient data registers, and so on. People agree very well that we should collect biological materials in the same way that we should have technical platforms producing results that can be compared between different centres, that we should have patient data registers that can also be compared and that we should be able to harmonise outcomes. But the problem is mainly economic. We are talking about infrastructure in 15 different areas," he says.

Convincing the commission

The reasoning behind Ringborg's argument seems to have hit the mainstream in Europe's cancer research community. Since 2005, the International Agency for Research on Cancer has been pursuing an initiative called Eurocan+Plus aimed at better coordinating cancer research and care in Europe by thrashing out some of these issues. Recognising that cancer research in the EU is fragmented and frequently duplicative, the project was set up in 2005 to identify specific barriers to collaboration and ways to overcome them. After two years of intense consultations, the final report of the EC-funded study identified six areas in which cancer research was being held up and chief among these is the issue of fragmented infrastructure, funding and priorities.

While the results of Eurocan+Plus have yet to be made public, many of those who were involved in the initiative have seized on the findings and are already pushing the agenda forward with the hope of winning the financial and political support of European Commissioners for rapid change.

In November last year, just as Eurocan+Plus' findings were starting to filter through to researchers and managers in the EU, 19 of the most influential cancer centres came together to debate the next steps. The result of their deliberations was a document entitled the Stockholm Declaration, coordinated by Ringborg along with Julio Celis, director of the Institute of Cancer Biology at the Danish Cancer Society, calling for immediate action to create a network of basic and clinical research centres to start the process towards greater cooperation and harmonisation across the EU. One of the key tenets of the Declaration is that, because the infrastructure already exists, visible improvements should be possible within a few years.

Perhaps the most important outcome from these community-wide discussions about cancer research, says Ringborg, is that for the first time, all stakeholders in European cancer research seem to have a common position on the challenge of improving research outcomes. And this unprecedented unity should help push the Commission into supporting the sentiments of the Stockholm Declaration and Eurocan+Plus. He cautions, however, that solving the fragmentation problem still presents a bit of a catch 22 situation. It is a necessary step to ensure funding from industry, but a large injection of cash is needed first to glue these networks together. "What will be costly is the next step," he says – actually bringing about change. He believes the final sum could amount to €15–20 million per year over a number of years. "We are talking big money," he says. Time will tell whether this need for substantial investment is, as with many pan-European dreams, too great a barrier to overcome.

THE STOCKHOLM DECLARATION

Signed by 15 leading organisations from 10 European countries, the Stockholm Declaration sets out a shared vision and commitment to tackle the fragmentation of Europe's cancer research efforts in order to "accelerate the translation of basic discoveries into clinical applications" and "improve diagnosis and care of cancer patients".

The signatories commit themselves to work towards "a collaborative platform comprising leading CCCs and basic/preclinical research centres in Europe" as the only possible way to reach a critical mass and sustainability necessary to innovate and deliver in all areas of cancer research.

While membership of the collaborative platform will be limited to centres fulfilling certain criteria, the Declaration signals a commitment to help bring in new insitutions by disseminating knowledge and strategies that would help them fulfill the membership criteria.

The Stockholm Declaration was signed by:

Belgium: Institut Jules Bordet (Dominique de Valeriola), **Denmark**: Institute of Cancer Biology, Danish Cancer Society (Julio Celis), **France**: Institut Gustave-Roussy (Thomas Tursz), Institut Curie (Sergio Roman-Roman), **Germany**: German Cancer Research Center, (Otmar D. Wiestler), **Italy**: Alliance Against Cancer (Angelo Paradiso), European Institute of Oncology (Gordon McVie), Fondazione IRCCS Istituto Nazionale dei Tumori (Marco Pierotti), **Netherlands**: Erasmus University Medical Centre (Alexander Eggermont), the Netherlands Cancer Institute (Anton Berns), **Norway**: the Norwegian Radium Hospital Comprehensive Cancer Centre (Anne-Lise Börresen-Dale), **Spain**: CNIO (Mariano Barbacid), **Sweden**: the Karolinska Institute (Ulrik Ringborg), **UK**: CRUK Cambridge Research Institute (Bruce Ponder), Christie Hospital Manchester/Manchester Cancer Research Centre (Chris Harrison), University of Oxford (David Kerr)

Source: The full text of the Stockholm Declaration was published in Molecular Oncology (2008), doi:10.1016/j.molonc.2008.03.004

How Europe is taking on the big biobank challenge

Marc Beishon

Cancer research is being held back by a shortage of high-quality, well-documented biological specimens. However, convincing hospitals to pool their specimens in a regional, national or international biobank is not always easy, adding to the logistical, technical, ethical, legal and IT obstacles of such a venture. Little by little, it seems, Europe is getting there.

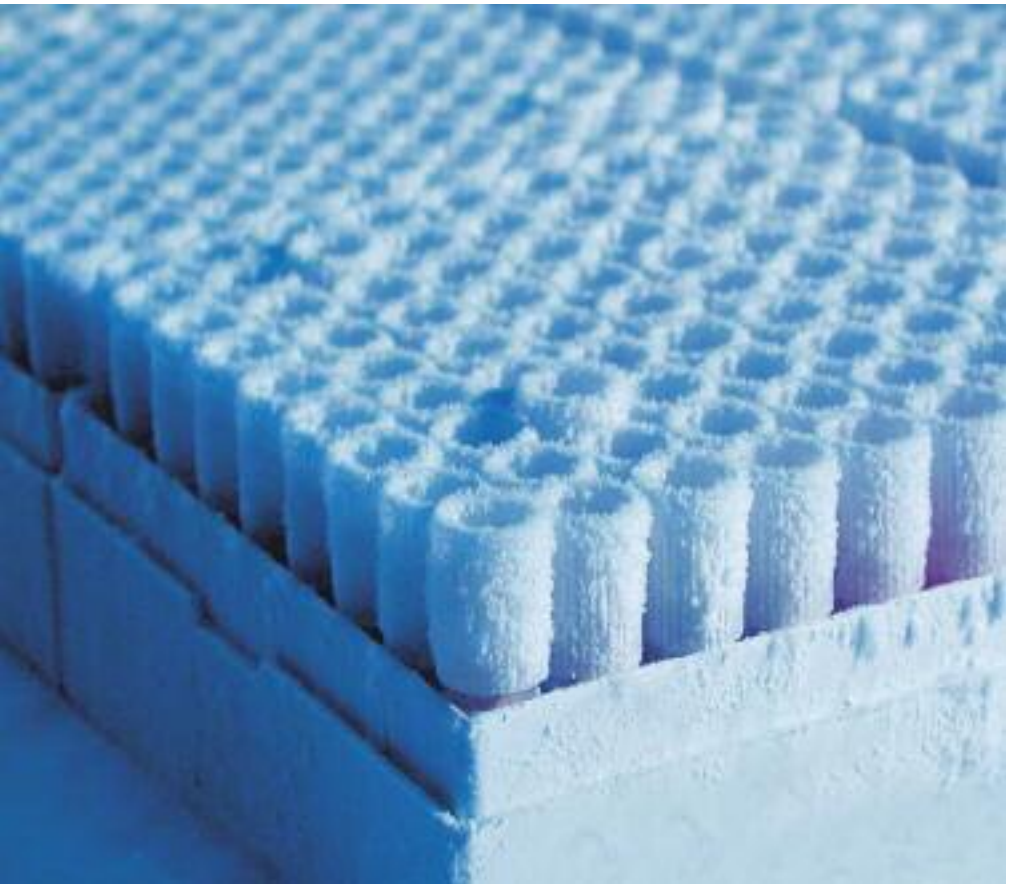
Techniques such as molecular analysis have the potential to lay bare many of the deepest secrets of cancer. But realising that potential requires access to large-scale, high-quality repositories of human biological material, linked to well-documented clinical histories. Known variously as biobanks, biospecimen repositories and tissue banks, there is now a great deal of activity in setting up the sort of standardised libraries of human samples that are necessary for keeping pace with the demands of researchers.

The terminology can be confusing – tissue banks are also used to store material used in transplants, while the term 'biobank' is now being applied to a new generation of population repositories, such as the UK BioBank, which will be taking blood and urine samples randomly from as many as 500,000 people, with a view to identifying genetic and environmental predisposition to a range of diseases, including cancer. There are also population biobanks dedicated to cancer research, but there are more disease-oriented banks in cancer, where a variety of specimens are taken during diagnosis and treatment. The term 'tumour bank' most accurately describes this type of repository, which often also collects unaffected samples for use by cancer researchers. But the various terms are used interchangeably, and 'biobank' seems to be the favoured word for any type of facility.

There is of course nothing new about collecting specimens – that goes back to the dawn of medicine – and for cancer there are probably thousands of banks around the world of various sizes and of vastly varying organisation and quality. Until recently there has been little concerted effort to lay down standards for tissue collection and storage for research purposes, or to unite collections for greater power in conducting studies. But the uses for well-organised biobanks are now compelling, and include the identification of biomarkers, identification and validation of targets in drug development, and linking disease-based resources with population biobanks and registries.

And while doors have opened with the introduction of techniques such as fluorescent hybridisation and tissue microarrays and the spectacular growth and potential in fields such as genomics and proteomics, others have been closed or are hard to shift, especially the minefield surrounding issues such as informed consent and the uses to which tissue can be put, which differ widely around Europe. Major scandals such as the retention of children's organs by hospitals in the UK without the knowledge of parents have, though, led to new regulations governing the use of human tissue in the UK and at European level, but it will be some time before rules and public views about biobanking are harmonised around Europe, if at all.

That has not stopped the launch of one of the most ambitious programmes yet in world biobanking – the Biobanking and BioMolecular Resources Research Infrastructure (BBMRI, www.biobanks.eu), one of six priorities for biological and medical research identified by the European Strategy Forum on Research Infrastructures. The BBMRI is coordinated by Kurt Zatloukal, professor of pathology at the Medical University of Graz, Austria; its



Frozen assets. A tray of specimens from the BioResource-Med tumour bank in Graz, Austria

preparatory phase is being funded by the European Union's Seventh Framework Programme.

European infrastructure

"It is important to note that this is the first time the European Commission has considered research infrastructures for life sciences, and that this is different than other European research projects, where there is participation from some member countries but no coverage for the whole of Europe, as has to be case for research infrastructures," says Zatloukal. The aim, he says, is to include as many existing biobanks and new projects as possible, in order to achieve sufficient sample numbers and appropriate coverage of Europe's populations. At the time of the project's kick off, in February this year, there were 52 project partners and more than 150 associated organisations from 21 countries – most with biobanks, some with other biological resources and tools.

The overriding aim is to generate much larger sample sizes to power studies, and while the BBMRI will cover all diseases, cancer will be a major application. But the need for the project goes much further, adds Zatloukal. "Currently, if you perform a study within a multinational collaboration, it is very difficult to know the legal and ethical contexts across Europe pertinent to the project partners. If we help establish this knowledge and provide guidance, everyone will benefit. Furthermore, even if you identified the right biobanks and got through the regulatory hurdles, you still have the problem of combining different samples often collected by following different protocols, which may be a severe problem for your study. Our aim is also to harmonise quality standards to ensure materials can be better combined in research."

These collaboration and quality issues are echoed at country level, and any pan-European initiative will also need the support of national programmes to help participating centres to raise standards to the necessary levels. In Austria, Zatloukal says that Graz has had one of the better organised biobanks for some time (called BioResource-Med, www.bioresource-med.at). "We provide a centralised pathology service for a whole region, with good standardisation and access to patient medical data, and samples have been processed in one institute under the same conditions for more than 24 years. We have tissues of nearly 800,000 people and 3 million diseased organs. That's one of the largest in Europe – although we do not know for sure, as there is no proper inventory. Improving knowledge of existing biobanks in Europe is one of the early aims of the BBMRI."

"Until recently there has been little concerted effort to lay down standards for tissue collection and storage"

Just a few years ago most cancer biobanking activity was isolated and far less organised than in Graz. Many collections have grown up as a project of certain researchers, and stored in everything from optimal conditions with proper documentation down to filing cabinets in a dusty basement corridor. Indeed, it is not unusual for some banks to be destroyed or simply forgotten when a researcher dies or moves on. The emergence of more organised structures has been led by a number of dedicated people, pathologists in the main, but also others such as molecular biologist Peter Riegman, who in 2001 became tissue resource manager for the Erasmus Medical Centre Tissue Bank, part of the molecular diagnostics unit of the Department of Pathology, at the Erasmus Medical Centre in Rotterdam.

"There was a biobank run by a pathologist on a volunteer basis, but it was not professionally organised," says Riegman. "Here I found an environment where I could use my research expertise, in combination with my informatics skills, and found a strong advocate in Wolter Oosterhuis, the head of the Pathology Department at the Erasmus Medical Centre, whose main research interest is germ cell tumours, and who had established and explored a bank for testicular cancer. We got financial support for a formal bank for the department, but I found there was little information then about how to run one."

Since then, Riegman has built a local bank in Rotterdam and also become heavily involved in the international biobanking community, in particular leading TuBaFrost, a project set up in 2002 with EU funding, and put forward by the Erasmus Medical Centre together with the EORTC (European Organisation for Research and Treatment of Cancer) and the OECI (Organization of European Cancer Institutes). TuBaFrost provides a central European database specifically of frozen tumour tissues, with participants that have made major contributions to EORTC trials. It is now under the wing of the OECI, to be used as a basis for a cancer research platform.

At Erasmus, Riegman says he now collects about 3,000 frozen samples a year, and 2,500 are given out, with 15,000 as a steady state. Anonymised clinical data are available for some projects. He also banks the routine pathology archive of formalin fixed and embedded tissues, which has accrued about 2 million blocks over the past 10 years, and he is participating in a national programme in the Netherlands, which will involve integrating electronic patient records. Together with chairing TuBaFrost and involvement with other forums, Riegman has one of the best overviews of biobank standards and how regulation on patient confidentiality and consent differ around Europe.

Centralised or networked?

While countries such as the Netherlands are still in the process of formalising national biobank structures, others have made substantial progress. Two models appear to be emerging for country-level cancer tumour banks in Europe – a national central repository, as in onCore UK, and a federated network with no central bank, as run by the Spanish National Cancer Centre (known as CNIO). The latter is seen by some as more challenging to run – collaboration involving remote locations often being difficult for any project. But the Spanish National Tumour Bank Network is now known in biobank circles as a great success, not least because of its director, Manuel Morente.

"As a pathologist, tissue collection, storing and custodianship have been an important part of my clinical activity for more than 20 years, and work with Spanish lymphoma study groups showed me how important well-preserved samples and associated data are for research," says Morente. "In 2000 I was invited to take a position in the new CNIO to create a collaborative network of hospital tumour banks, and I believe it is the first of its design in the world."

The CNIO networks both basic and applied researchers – "It was my first direct contact with basic science groups and I saw how difficult it is for them to obtain high-quality samples," he says. "Every Spanish hospital is invited to collaborate, and our network is open to the entire scientific community. I feel it

QUESTIONS ONLY BIOBANKS CAN ANSWER

- Is the genetic change I have identified in cell lines expressed more in cancer than in normal tissue?
- At what stage is my gene expressed – early- or late-stage disease?
- Is my gene of interest expressed in one type of cancer or lots of types?
- Can I detect my object of study using paraffin material as well as frozen?
- Can I find a molecular or protein pattern that correlates with clinical outcomes or response to therapy?
- Can I subdivide my chosen cancer type on molecular grounds better than I can with conventional pathology?
- Can I predict from a blood sample whether someone is likely to develop cancer?
- Can I detect from a blood sample whether my patient is going to relapse?
- Is the molecular biology of a particular type of cancer related to inherited genes, the age of the patient at diagnosis or exposure to a particular agent?

Source: Gerry Thomas, director of scientific services, Wales Cancer Bank

"It is not unusual for some banks to be destroyed or simply forgotten when a researcher dies or moves on"

works because of the simplicity of the design and respect for the role of hospitals and pathologists."

Banks and samples remain with the hospitals, but Morente says they are now following the same procedures and quality control policy under central coordination using a computing platform developed for the purpose. "The role of our coordination office is to promote, coordinate and harmonise procedures – and to form relationships with our end users, the researchers. But the initial challenge was to obtain cooperation from pathologists and clinicians, because there was no previous expertise in biobanking in Spain."

Any Spanish cancer research team can now request samples from the National Tumour Bank Network. They send a summary of the project, outlining the funding sources, along with a completed tissue request questionnaire. "We also offer an advisory service to help researchers, mainly in non-clinical groups, to design better projects," says Morente.

Once the participation of the National Tumour Bank Network has been approved by the ethics and scientific committees at the CNIO, Morente's team then finds sufficient cases in the central database that suit the project and arranges to send them to the research team.

"We carry a mirror of each hospital's database of tissue samples – these make up our central database," he explains. "Hospitals receive details of the project, the principal investigator and the funding agency, and it is their choice whether they collaborate or not. If they do, they send the samples to the central office where they are checked for quality and anonymised again, if necessary."

The output from the network has been growing. "From 2001 to 2007, we provided support for more than 250 projects, 58 in 2007.

The Spanish National Tumour Bank Network is now supported mostly by central government funds, having proved its worth after getting off the ground through various other funding sources. It has also 'cascaded' expertise around Spain – Morente says four regional networks are now in place that share the principles of the central organisation.

Another measure of the Spanish success is the influence on other national cancer biobanks that are now springing up around Europe, and also further afield. Biobank Ireland, a recent tumour bank networking project for both the Irish Republic and Northern Ireland, is modelled on the Spanish network, and will be bringing up to 11 hospitals into the project. Morente is also involved in a tumour bank platform in Latin America.

In the UK, a model where tumour samples are stored centrally is in its early stages of development. onCore UK, says its chief executive Brian Clark, is unusual in being a standalone, neutral charity. "A traditional way to set up a national resource such as a biobank would be to make a grant to a lead university and ask it to set one up, but after the loss of trust we had in the UK over the organ retention scandal, the funders felt it was important to set up an arm's length, independent organisation – but of course our only source of samples are patients in the NHS."

onCore UK has contracted a commercial firm to store tumour samples, which are collected 'opportunistically' from a network of participating hospitals. "We are taking blood samples, which are processed into constituents such as white cells and serum, and pieces of cancer and also unaffected tissue where possible. We are only taking new materials – I am

Co-ordinator in chief. Pathologist Manuel Morente spearheaded the National Tumour Bank Network in Spain. It uses a centralised IT system and harmonised procedures, but specimens are stored at the hospitals where they were harvested

keen to stress that we are not taking over or replacing existing UK biobanks, but supplementing them. This is not a competitive environment as there just are not enough high-quality samples available for research. It is also a long-term project – there are no quick wins in biobanking. It is a slow and arduous process."

onCore UK is a member of the NCRI (National Cancer Research Institute) Confederation of Cancer Biobanks, a networking organisation in Britain, which aims to share expertise, harmonise standards and assist access, with a pool of samples (it recently announced a portal for searching for samples held by members). Another member is the Wales Cancer Bank, launched in 2004, which is in the Spanish camp as a networked model. Indeed Gerry Thomas, director of scientific services at the Wales Cancer Bank, contends that a centralised approach could cause resentment. "You only have to look around to see that the models that work take the virtual approach, but they do have to be served by a central IT system," he says.

Promoting participation

Participation in either a networked or centralised model can be difficult to promote. At a European level, Zatloukal comments, "My view is that even more critical than trying to bring together biobanks working on varying standards is addressing the question of why researchers should make their collections available in a European context. There is a strong sense of local ownership by individuals and organisations. We have to say very clearly what the benefits of sharing are and perhaps put forward incentives such as being a preferred partner for future studies or for certain funding."

Riegman also reports problems with TuBaFrost, which he says "is not functioning as well as I would want. People say they are interested, but not many samples are being put forward." He is pleased that the OECI's accreditation initiative for cancer centres plans to use, as a quality benchmark, the requirement that every centre should have a biobank that is involved in international exchange [see also Grand Round, p14].

Clark argues that the success of a biobank is "not the number of samples but the number of outgoing samples and projects supported,"which he believes centralised models are better able to support. He feels that the BBMRI project, though laudable, will be very hard to operate effectively, and considers that onCore UK's independent status and participation in cooperative groups will avoid the problem of lack of 'buy in' from the research community. "I did not want to repeat the lack of cooperation that some decentralised projects have had. I see onCore UK as like our blood transfusion service – a separate organisation that relies on collection in many places and with central storage. It is a trusted partner – but that did not happen overnight."

onCore UK, adds Clark, also has the advantage that the NHS is good at collecting routine patient data, and electronic subsets will be available for integrating with tumour samples. "A limitation of some tumour banks is that associated patient data is just a snapshot, and their ability to collect longitudinal data is very restricted," he says.

There are many other biobanking projects either directly related to or associated with cancer. Smaller groups working on rare cancers have a particular interest in international biobank projects. Riegman mentions EuroBoNet, a cooperative group working on bone tumours, which he has been working with, helping to assemble a virtual bank of tumour specimens and cell lines. Europe's leukaemia research groups are also heading in the direction of pan-European biobanking [see Spotlight, p 42].

Though all this is still at a fairly early stage, Europe is ahead of the US on large-scale cancer biobanking, especially with networked projects, and is likely to remain in the lead for some time. The National Biospecimen Network mooted by the National Cancer Institute in the US is still in a conceptual phase, although a pilot for prostate cancer has been launched and there is activity on

MARIA DIAS

Information retrieval. Biorepository technician Gemma Bullock removes samples from one of the freezers at onCore UK's centralised storage facility, in Hertfordshire

"There is a strong sense of local ownership. We have to say very clearly what the benefits of sharing are"

fronts such as best practices for biospecimens and a specimen locator (see http://biospecimens.cancer.gov).

The slow progress in the US has led to advocacy organisations stepping in with their own initiatives. The Multiple Myeloma Research Foundation (MMRF), led by the dynamic advocate Kathy Giusti, launched its own tumour bank in 2005. Having first set up a research consortium among leading cancer centres, such as the Dana-Farber Cancer Institute, the MMRF set about obtaining a significant volume of high-quality bone-marrow biopsies and peripheral blood samples, and says it has created the only resource of its kind in the US.

"It integrates patient tissue samples with corresponding genomic and clinical data, enabling researchers to identify and validate optimal molecular targets for myeloma and drugs active against these targets, as well as conduct correlative studies to determine patients' responses to current and emerging therapies," reports the MMRF.

One recent use of the bank includes a genome mapping programme that reported finding genetic similarities among certain types of multiple myeloma, following analysis of nearly 100 tissue samples. These data were released last December at the same time as the launch of the Multiple Myeloma Genomics Portal, said to be a world first.

Other US groups taking a similar approach include the Lance Armstrong Foundation, which is funding a germ cell tumour bank in Los Angeles for national access, the Inflammatory Breast Cancer Research Foundation, and Mary Ellen's Tissue Bank (also for breast cancer).

Ethical issues

In Europe, the German breast cancer patient group Mamazone has done something similar, with the founding of the Patients Tumorbank of Hope (PATH). But European advocacy organisations are also addressing key ethical questions governing information, consultation and consent. Getting these right will be key to minimising unnecessary red tape while maximising patient participation.

Europa Donna, the European Breast Cancer Coalition, is canvassing members and becoming involved in national reviews on the use of samples, such as in the UK when the country's Human Tissue Act was consulted on. But this is unusual – a survey of members by Europa Donna revealed that in several countries there is still a system of presumed consent, and many countries do not yet have legislation specifically covering tissue banks. Europa Donna's UK group also ran a campaign to help explain tissue banking issues.

Bettina Borisch of the Institute of Social and Preventive Medicine, University of Geneva, says the public has fears about being "disposed by an authority outside one's own will", and says the very word 'bank' can confer images of property and profit. She stresses, however, that bottlenecks in clinical

The private banking sector

The commercial sector, of course, also has a strong interest in biobanking. Some firms collect specimens purely for resale to researchers; others are setting up repositories for their own research. There have been many new entrants in the first camp, mainly in the US, but according to Clark of onCore UK, their number is falling. "I believe that is because a biobank is more like a civic amenity – it is difficult to make a commercial model work," he says, adding that onCore UK offers its services to pharmaceutical companies.

AstraZeneca is an example of the second camp. Chris Womack, principal clinical histopathologist in cancer discovery, is very active in biobank circles. "We are looking for biomarkers that will show us proof of mechanism, and we use tissue arrays and immunohistochemical techniques," he says. "A lot of the information is already out there, but we need to build internal confidence in the published data, as well as investigating new targets and markers."

The company works closely with hospitals in preference to buying samples in from commercial suppliers, which Womack says can be variable in quality (and there are still plenty of suppliers – he lists 24 in a presentation). "Quality can suffer if samples have been left too long before being fixed in formalin, or if the formalin penetrates poorly. And hospitals have expertise in pathology and immunohistochemistry we can tap into."

research are worrying groups such as Europa Donna, and they are keen to support well-conducted studies with a high degree of transparency, such as the MINDACT breast cancer trial, which requires analysis of fresh or frozen tissue.

Another important aspect of biobanks is computing and bioinformatics. Biobank projects in Sweden are among the world leaders in the use of technology – for example in 2004 the Karolinska Institute partnered with IBM to build database structures to integrate research projects around the country, and automation such as robotic DNA extraction systems and sample dispensing systems are in place. Sweden also has a large national programme of population biobanks and registries, including the world's largest twins collection, and several long-standing tumour banks.

IBM itself has a strong interest in biobanking – it has developed a biobank information management system designed to integrate research data originating from many sources, and has been running worldwide biobanking summits. It is also one of the sponsors of BioBank Central, a US website (see www.biobankcentral.org), and has started a World Community Grid to provide computing power for analysing the output from tissue microarrays, as manual analysis is another major bottleneck.

Overcoming these bottlenecks will be essential to speeding up progress in cancer research. But an equally important challenge, according to onCore UK's Clark, will be getting the basic research community to shift from non-human alternatives to more relevant human tissues. "They often think they can work faster with other models," he says. Riegman agrees that the red tape for using human tissues is an obstacle. "People can simply give up rather than go through all the paperwork needed for permission to work on samples." TuBaFrost, he says, was originally designed to also support trials, but the narrow permission laid down by the European Clinical Trials Directive has changed its focus to become a more open access model for research on residual tissue left over after diagnosis. National and international lawyers are playing a key role in biobanking. "For TuBaFrost," adds Riegman, "the advice is laid down in a Code of Conduct for residual tissue, that the laws of the country of origin determine what you can do with tissue in another country. Accepting this principal for all human samples as a rule would cut down red tape enormously and also respect the laws from the country of origin and therewith the general democratic opinion of the donors of the country of origin. But people know which countries are 'difficult' and avoid them."

At this stage of the evolution of cancer biobanks, networking among professionals is vital. Morente notes that the most important organisation is the International Society of Biological and Environmental Repositories (ISBER), while a less formal group is the Marble Arch International Working Group, which is a group of international experts in biobanking management, currently with about 20 representatives worldwide.

There is also a growing discipline in the management and science of biobanking, which involves design principles, data protection, quality, long-term storage, identifying new fixatives for tissue, and the many other issues that determine what molecular biology research is possible. Agencies in France have been working on a national standard for biobanks based on existing ISO specifications, which the Marble Arch group is supporting as a possible model for an international standard. As Clark comments, "At present there is no obvious national or international standard against which research biobanks can implement their quality management system." The emphasis now, he says, is rightly on professionalising what has been a haphazard and low-priority area, and also securing long-term funding, dedicated staff and a strategic rather than a project-based purpose.

LOOKING FOR THE BIG PICTURE

A project that is linking both population and tumour biobanks with cancer registries is Cancer Control using Population-based Registries and Biobanks (CCPRB), an EU Sixth Framework Programme, and one of the largest initiatives of its type. Coordinated by Joakim Dillner, professor of virology and molecular epidemiology at Lund University, Sweden, it has linked large biobank projects with up to 30 years of follow-up and more than 60,000 prospectively occurring cancer cases, with cancer registries that have more than 40 years of population-based registration. There are 18 partners in the project from nine European countries.

Research highlights include a linkage of the Swedish cancer registry and multigeneration registry for assessment of familial risks for many cancers; a number of large-scale association studies within the participating biobanks for familial or sporadic breast cancer and colon cancer; and a linkage of maternity cohort biobanks with cancer registries, which has identified a large study base (more than 1,000 cases and 2 million controls) for intrauterine exposures and risk of childhood leukaemia.

Apart from medical research, the project has helped establish quality standards for linking biobanks and health data registries, and also the first formal graduate school in biobank-based epidemiology, as part of the European Programme in Public Health and Epidemiology. This is organised by the Public Health School at Tampere University in Finland.

The people's pharmacologist

Anna Wagstaff

Silvio Garattini gave up a glittering academic career to found his own set-up where research could be carried out free from commercial or political agendas. Today, the Mario Negri Institute and its founder play a vital role on the European scene, championing a 'rational approach' to drugs, and a research culture based on collaboration and transparency and led by patient need.

Silvio Garattini was only 33 years old when he led an exodus from the University of Milan's Department of Pharmacology to found a fiercely independent institute for pharmacological research, named after its financial sponsor, Mario Negri. The year was 1961, and Garattini must have known he was in for a bumpy ride.

Apart from robbing the University of some of its brightest and most motivated pharmacologists, the young upstart was consciously breaking ranks with a powerful medical and academic establishment that he saw as a closed fraternity, cut off from the needs of ordinary people, heavily dominated by political patronage, and quite incapable of fostering world-class scientific research.

Garattini and his colleagues were determined that the Mario Negri Institute would be different.

From the outset the founding members decided they would publish only in English, thereby locating the institute firmly in the world of international research – and guaranteeing opprobrium from Italy's citadels of academia, who saw it as a snub not just to them but to the whole country.

But they reached outwards towards the Italian people. Breaking with a long cultural tradition that excluded the media and lay audiences, the founders of Mario Negri defined 'dissemination of information' as one of three main areas of work, alongside research and training. Today, aged 80, Garattini still spends around 50 evenings a year addressing public forums, helping ordinary people and patient advocates understand and play a role in the processes that govern the way medical research is carried out and new treatments are made available.

They committed themselves to high levels of transparency – every piece of research undertaken would be published in its entirety. When Italy finally recognised drug patents in 1978, Mario Negri decided, in the same spirit, that it would not seek patents on anything developed within its walls.

They took a stand against the hierarchic power structures and career paths of the academic world. Researchers at Mario Negri keep no time sheets, and there is a pervading atmosphere of informality. Garattini himself dons a tie for no one. Whether he is busy with his prolific output of articles, at a formal ceremony to accept an award, making one of his frequent television appearances, or even showing the Italian President his new premises, he will be wearing his hallmark white poloneck jumper.

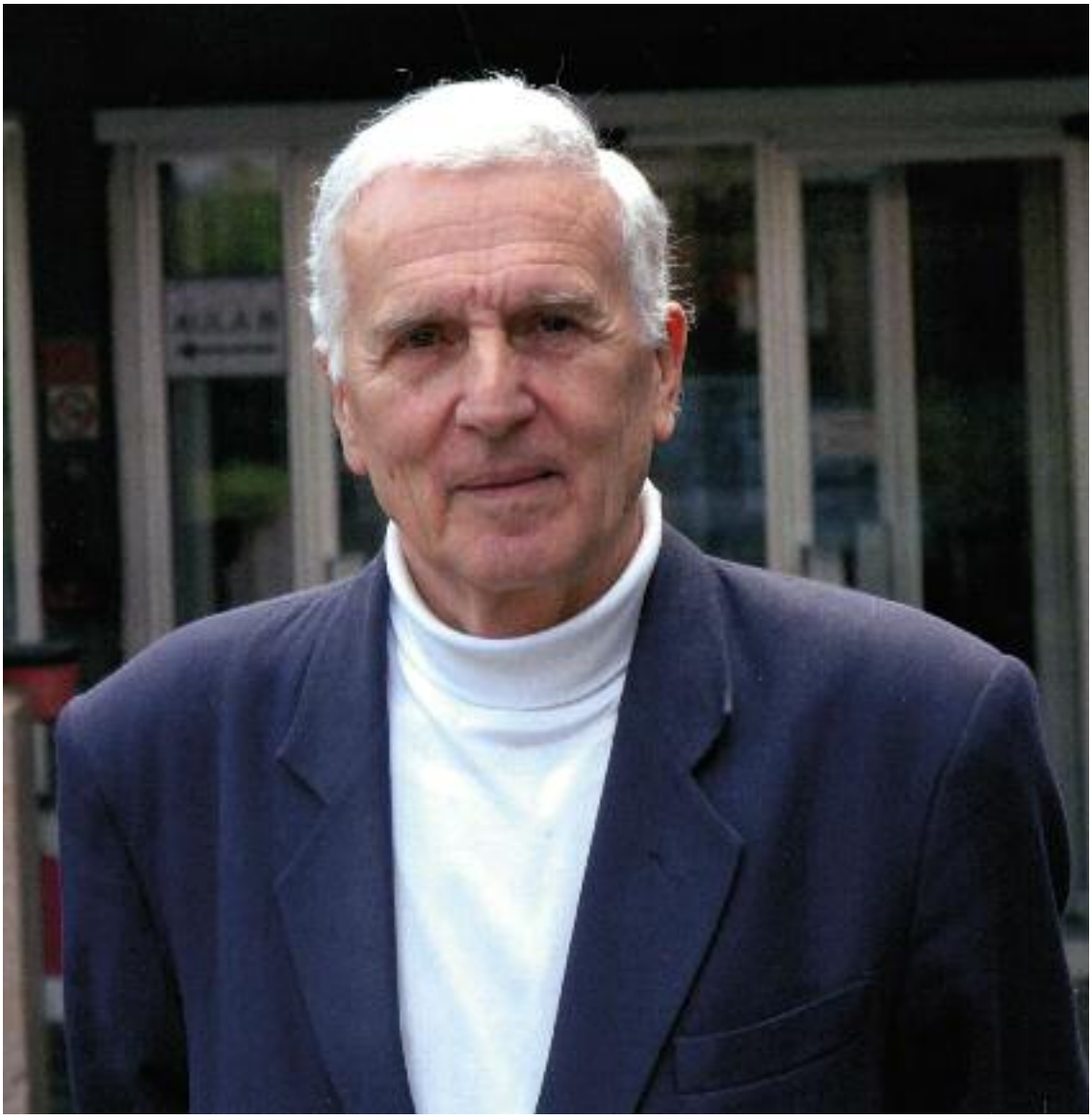
Above all, Mario Negri was to be independent – free from the political patronage and internal

politicking of the universities and free from the profit-making agenda of industry. To avoid becoming reliant on any single source of funding, they decided to limit the amount of any grant or contract to no more than 10% of overall income, condemning themselves to the constant pressure of finding a wide range of backers.

This was a vision so ambitious, it bordered on the audacious. And Silvio Garattini was one of the few people who could have hoped to pull it off. What was required was a mix of qualities that he happened to possess in spades: an exceptional academic standing, unflinching self-belief, a strong and infectious motivation, and a talent for communication.

Academic heavyweight

When Garattini convinced 21 of his colleagues to wave goodbye to the status and security of an academic career to embark on the Mario Negri adventure, he himself was in line to become Italy's youngest professor at the highly respected University of Milan. Having arrived at medical school



A rising star. Garattini aged 30, with Daniel Bovet, winner of the 1957 Nobel Prize for Medicine (right) and Emilio Trabucchi, head of the Department of Pharmacology at Milan University (left). This is the last known picture of Garattini in a tie

with a fully-fledged qualification in chemistry, he had soon come to the attention of the head of the Department of Pharmacology. "Every year the professor asks the students if any of them would be willing to give a lecture. I gave a lecture, I remember, on anti-histamines. I took advantage of my chemical background. I could show all sorts of structures showing which were the groups that showed activity, and the professor was relatively impressed and said, 'Why don't you come and work here?'"

Garattini was propelled at speed up the ranks, and within a few years was second in command and effectively running the department – his boss had been elected to Italy's national parliament and was almost permanently tied up with political commitments. By 1961 therefore, despite his tender years, Garattini was already an academic heavyweight with a strong following.

His rise to prominence was all the more impressive because he had made it as an outsider, and this no doubt contributed to his strong self-belief. He was the first in his family to attend university – his father worked in a bank, supporting him, his two brothers and his severely disabled mother. Lacking the money to go to university, he opted for a vocational school in Bergamo that offered a technical qualification in chemistry. "This was a real education. In the morning you had all the academic stuff, Italian, mathematics etc. In the afternoon you had to work in the lab, and you were judged on the basis of the precision of your analysis. This was the most important degree I got in my life."

His most important role model was his dad, who had himself been forced to make his own way in life, having lost both mother and father when he was only two years old. "He taught me to think critically, and not believe everything you see."

As for his motivation, Garattini talks not of a lifelong desire to help people or cure disease. He wants to do and facilitate excellent research aimed at providing solutions to real problems, unhampered by ulterior agendas. This drive was evident even in his first job quality checking the output of a local steel works in Bergamo. "I was in reality interested to see an analysis throughout the whole production process, but my boss said, 'You are not being paid for that. Don't do extra things.'" That job helped finance him through medical school.

"If we are serious about doing this research, either we go to the US or we do something different here"

"The universities predicted no young people would come – which turned out to be completely wrong"

Research as a profession

But it was not until he travelled to America, in 1957, that his vision for the Mario Negri began to take shape. "I was impressed by the fact that research was a profession. In Italy, if you were at the university you did research and you published because this was a way to get promoted. If you were in industry, of course you did research the industry required."

He came back to Italy bursting with enthusiasm. "I had a group of about fifteen to twenty people around me, and I said, 'If we are serious about doing this research, either we go to the US or we do something different here. And the idea was to do something in our country. With a lot of naivety, I asked all the persons and groups that might be interested, 'Why don't you help me establish a foundation?' Some people laughed. Some people were not interested. Some said: you are too young, you should stay at the university."

In the end, it was an Italian industrialist who had made a fortune manufacturing affordable jewellery who gave Garattini the backing he required. Mario Negri had invested part of his fortune in small pharmaceutical companies, and came to Garattini for advice on the logistics of getting a new drug approved. They got talking, and the upshot was that Negri agreed to support the idea of a research foundation. Before anything concrete had been settled, Negri was diagnosed with liver cancer. A couple of weeks before he died, he rang Garattini, assuring him that the project they had discussed would be provided for. And sure enough, when the will was read out, 900 mn lira had been set aside to establish the Mario Negri Institute for Pharmacological Research. Garattini was named in the will as director.

The new kid on the block received a frosty reception. "We had a lot of hostility from the academic milieu. This was the first time the universities had to deal with something that was not a university, and they predicted that no young people would come to us – which turned out to be completely wrong."

That Mario Negri survived its first decade was largely thanks largely to generous grants from abroad – the Wellcome Trust in the UK, the US National Institutes of Health, the US Army, Navy and even the US Department of Agriculture. When the institute wanted to offer degree courses, no Italian university would partner them – so young researchers at the institute now study for a PhD in pharmacology from the Open University in the UK.

Pioneering innovations

The Mario Negri has grown into a world class research institute. It has published more than 10,000 articles in international scientific journals and trained more than 3,000 young scientists. Four of the 50 most frequently cited Italian scientific researchers (across all disciplines) are based there. The original group of 22 has grown to more than 900 spread between the headquarters in Milan, Garattini's home town of Bergamo, and Abruzzi, southern Italy. Last September, Garattini and his colleagues bade a fond farewell to their old headquarters, and moved to a new building accommodating 24,000 m^2 of state-of-the-art laboratories. An inaugural visit by the President of the Republic indicates the pride Italy now takes in the Mario Negri.

Iain Chalmers, editor of the James Lind Library and one of the founding spirits behind the Cochrane Collaboration, argues that the influence and achievements of the Mario Negri cannot be measured only by what goes on within its own walls.

He says that the non-profit, patient-needs-driven model championed by Garattini has enabled Mario Negri to help bring about a number of important innovations in medical research. "It was the Mario Negri Institute that organised the first mega trial of a treatment, the GISSI I study, which demonstrated that streptokinase decreased mortality in patients with myocardial infarction. This study covered 90% of coronary care units in Italy – thousands and thousands of patients. They don't get proper credit for that."

A source of national pride. Garattini showed President Giorgio Napolitano round the state-of-the-art laboratories at Mario Negri's new headquarters last December

He also credits the Institute with fostering the development of the methodology for studying adverse effects once a drug is in use. "The Institute convened a meeting of all the international pioneers in the field. The report – *Epidemiological Evaluation of Drugs*, published in 1977 (Colombo et al.) – is a seminal book, which we celebrate in the James Lind library."

Looking back at the development of the European medical research scene over the past decades, there are few people who have had such widespread influence as Garattini. Indeed, he remembers as little more than a minor footnote his role in founding the European Group on Cancer Chemotherapy (now the European Organisation for Research and Treatment of Cancer), in 1962, together with two great pioneers, Georges Mathé, from the Institut Gustave Roussy in Paris and Henri Tagnon, from the Institut Jules Bordet in Brussels.

"At that time very little research was being done in cancer. It was generally not considered suitable for drug therapy. So one of the reasons for establishing this group was to raise interest in industry." As it happens, he says, industry quickly twigged that there are big profits to be made in cancer, because it is such an emotive disease. "In many cases drugs are promoted even if they are of little activity – it's enough that a couple of newspapers say: why is it not available?"

His big concern is that many diseases fail to attract that sort of interest. A similar initiative for collaboration in the field of atherosclerosis, failed to stand the test of time. "I tried also other things, but they didn't function. I think cancer is an essential area, but I have widespread interests. I am very interested in rare diseases and orphan drugs, because I believe this is part of equity. It is not good that people with rare diseases are left to their own devices." Sixteen years ago Garattini helped address this unmet need by adding to the Mario Negri a centre for clinical research in rare diseases, named after its sponsors, Aldo and Cele Daccò. Located in Bergamo, it is the first such centre ever to combine education, information and research.

Promoting innovative drugs

The unique model of the Mario Negri has provided Garattini with an independent base to argue for 'rational' approaches to developing, regulating and reimbursing medicines. He has sat on countless national and international committees, and everywhere he goes he argues for certain key principles.

One of these is that it is a moral and scientific imperative that all data from all clinical trials – negative as well as positive – should be made public, and that a failure to do so results in patients being prescribed ineffective drugs. This issue recently hit

"I am very interested in rare diseases and orphan drugs, because I believe this is part of equity"

"It would take only two words to be inserted in the legislation: new drugs must show 'added value' "

the headlines (again) with respect to selective serotonin response inhibitors (SSRIs). Another is that new drugs should only be approved for the market if well-designed studies – preferably at least one of which is conducted by an independent trials group – show they are better than what is already available. He wants to see an end to non-inferiority trials.

One of his more high-profile public roles was thrust upon him in 1993, following a major scandal that saw many drug company officials, civil servants and even the Italian health minister jailed for corruption over drug reimbursements. Garattini was appointed to a committee to review the entire list of drugs on Italy's national health service formulary. "Together with others, we cleaned the whole thing up. We removed all the products for which there was no scientific evidence and decreased the expenses of the state by 4000 bn lira – from 13,000 bn lira to 9000 bn lira."

Denying patients access to obsolete medicines proved a tricky business, and doctors – with no small encouragement from the industry – put up strong resistance. Garattini responded by taking his case to the public. "I did a sort of tour of Italy to explain why there was this change, and participated in a large number of debates. It was very interesting."

Timing, he recognises, was the key to his success. "The public was ready for a change, because they were indignant about the corruption. If it wasn't for that, it would probably have been impossible to change. You must pick the right time to do things."

When control over which drugs gained entry to the Italian market was ceded to the European Medicines Agency (EMEA), Garattini took his arguments onto the European stage. The current set-up, he argues, favours the interests of industry over patients. "I would like to see EMEA under the control of DG SANCO, where they talk about health, while today it is under the control of the DG for Enterprise and Industry, which is illogical."

He is also strongly critical that new drugs can be approved even if they are no better, or even less good, than what is already available. "There should be legislation that favours the approval of useful drugs, not the approval of anything that shows quality, efficacy and safety. It would take only two words to be inserted in the legislation: new drugs must show 'added value' – this could be greater efficacy or less toxicity or better compliance, whatever. You could make a rule to say you have to compare against the optimum treatment available."

He has backed up his arguments with studies showing that the majority of cancer drugs approved by EMEA in its first 10 years failed to show the level of evidence of efficacy required even by EMEA's own guidelines. Despite these arguments, recent changes to the regulations, which introduced the option of 'conditional approval', lowered the bar yet further.

Has Garattini finally met his match? He doesn't seem to think so. Despite his advanced age, he argues that time is on his side. Sooner or later, he says, Europe's health services will no longer be able to cope with a constant stream of new drugs that add little benefit and cost the earth. Earlier this year he helped launch a pan-European collaboration "for the rational use of medicines". Hosted in Piperska, Stockholm, by the Karolinska Institute, Stockholm County Council and key personnel from Mario Negri and the Universities of Heidelberg, Liverpool and Marseilles, it was attended by healthcare professionals from nine EU countries.

"We will issue a paper, and go back to governments to argue the case. You have to continuously spread the idea. I repeat it everywhere. Little by little there will be somebody else, and then something will happen."

Timing, as Garattini has learnt, is key. "I believe that people and organisations in general are not very rational. You need to have some special event that will shock the people and determine a change. I am waiting for the moment when the system becomes unsustainable, which will probably not take much time. That is the moment at which you say, 'OK you have to change.'"

"There's a shadow in your head"

Eric Baumann, a healthy 34-year-old, in love with life and his new girlfriend, had just started as the new London correspondent for the Swiss daily *Tages-Anzeiger* when he was diagnosed with brain cancer. His description, republished here, of the seven tumultuous days that changed everything, and how he still manages to retain his love of life, won him a Best Cancer Reporter Award.

Wednesday 29 December 2004. I'm lying on a bed in the emergency room of Zurich University hospital. It's just before midnight. In a few minutes I'll turn 34. A salty solution is flowing into my arm. I wait impatiently for the result of the X-ray. Hopefully this fuss will soon be over. Then I will celebrate my birthday with some friends. It can't be anything dramatic. Pulse, blood pressure, reflexes – all OK. It's just that headache.

I see four doctors coming towards me. Their faces are gloomy. "There is a shadow in your head," one says. "It could be an infection – or a brain tumour." My girlfriend squeezes my hand, shocked. I want to wake up from this nightmare, but I am already awake.

I'm only supposed to be in Zurich for a couple of days. In early December, I flew to London to start a new job as a correspondent for the Swiss *Tages-Anzeiger*. It was tough at first. Finding a flat seemed impossible. Above all, I missed my girlfriend – we had met in August.

Eric Baumann

One week after arriving, bad headaches woke me up in the night. It was not a hangover and I never had migraines. I thought the new environment and the distance to my fresh love was to blame. Painkillers brought relief for a couple of hours. I wrote articles and found a small flat in London's East End. The first evening I wanted to inaugurate my new place with a glass of wine in the bath. A headache attack got me out of the water.

Headache was not the only symptom. Since July, several times I had completely lost my ability to speak for a few minutes. I knew what I wanted to say, but I couldn't catch the words, they just danced around me. I blamed it on stress and heavy partying. Months later doctors told me this is called 'speech arrest' – very common with brain tumours.

Around Christmas I flew back to Switzerland. On Christmas day I went to see my general practitioner. He confirmed the headache could be linked to my disc damage. He prescribed a tranquiliser.

In the evening, I went to my brother and his wife, we celebrated together with my father. It was the third Christmas without my mother. She died of cancer in 2002.

When I had woken up on this Wednesday, lines appeared in zigzag on my

Tages Anzeiger

DAS MAGAZIN

left eye. I booked an appointment with an eye specialist. Then I went to have lunch with a friend. The headache came back, I felt dizzy. I asked for the bill – when the waitress came I saw her twice.

The eye specialist seemed to think I was a hypochondriac. He said the eye problem and the headache were not connected, and prescribed some drops.

I felt a bit better in the afternoon, but my girlfriend urged me to go to the emergency unit. There they X-rayed my head.

Thursday 30 December 2004. Six in the morning. A nurse opens the curtains. It's still dark outside. At night they had pushed me through a tunnel system to the neurosurgical ward. That's when I became a patient for the first time.

I get up, rubbing my eyes. My roommate is an old man – he's in good spirits: "Breakfast is the highlight of the day!" I would like to hide somewhere.

I'm glad when they come to pick me up. I'm wheeled through the hospital complex, from one test to the next. I still can't believe what's going on. I'm so shocked by it all and befuddled by medication that I haven't yet worked out what impact this will have on my life. Will my girlfriend stay with me? How will my friends react? Who tells my office? How long will I have to stay in hospital? But I'm aware that this is so big I can be happy just to be alive.

I have to get into a tube for an MRI. The machine cuts my head into virtual layers and turns them into negatives. When I see them, I choke. On the left temporal lobe I can easily spot the long, white shadow a doctor had mentioned the day before. An enormous swelling surrounds it, trying to protect my brain. However, space in a head is limited. Its content is being squashed to the right. No doubt, it's a brain tumour, says the senior doctor. Its diameter is four centimetres and it is spreading in all directions. I need an operation as soon as possible.

On the magnetic resonance image, I see my birth date: 30-12-1970, and the date of the picture: 30-12-2004.

Until now I used to think, 'how tragic', when I heard of diseases like this. I considered myself to be so fit and healthy I was convinced I would never have to face such a fate. Now I have to deal with an expanding growth in my body, with my own cells revolting against me. It's happening in my brain, the centre of my personality.

I'm too exhausted to deal with all the people trying to contact me and ask me questions. Yet it's so important for me to see they care. Their support gets me through these days. My girlfriend is the biggest help. She spends as much time with me as possible; she waits this and every evening in the hospital room until I'm asleep.

Friday 31 December 2004. I'm being pushed to more tests in a wheelchair. Cortisone reduced the swelling in my head. The pain is gone. Even the zigzag lines are less visible.

In the afternoon I am informed about the operation. It will take place in three

"The eye specialist seemed to think I was a hypochondriac. He prescribed some drops"

"The word 'latency' will always remind me of the days in hospital that turned my life into before and after"

days: January 3rd, Monday morning. Yashuro Yonekawa, director of the neurosurgical clinic, will do it. For the first time I hear that I won't be fully anaesthetised. Maybe I got something wrong.

Sunday 2 January 2005. If the situation were different, I would return to London today. Instead, I have an appointment with the surgeon. He tells me I'll be awake during the operation. So I did get it right. If it's not clear whether cells are part of the tumour, a mild electric shock will be put on them and I will be asked questions at the same time. If I answer late or not at all, they are important. This way they can avoid cutting too much out.

To think of my skull being opened is scary enough. Witnessing it makes things worse. At least the surgeon has an international reputation, I'm told. I must sign a contract listing meticulously all the risks of the operation. I don't feel like reading it.

The night shift nurse tells us some nasty anecdotes from the operation room. I don't mind. He makes me laugh several times and makes it feel as if I am on the staff side and not a patient. Later I take a sleeping pill for the first time in my life.

Monday 3 January 2005. Woken at six again. Under the shower I think this is the last private moment before my execution. Before the operation, a speech therapist tests me to check how long I take to answer questions under 'normal' circumstances.

A doctor puts a catheter into my chest. He injects pain killers and a mild anaesthetic. I can't feel that my head is being screwed onto the operation table. Nor that somebody is cutting a half moon into the skin on the left side of my skull. The cut part is laid over my ear. A quadrangle the size of a playing card is sawn out of the bone, wrapped up in gauze and put into a chromium bowl.

During the operation, I doze. It feels as if there is an empty box in my head and somebody is poking at it with a spoon. In fact it's the surgeon, removing tumour cells with a mini vacuum cleaner.

The closer the surgeon moves to the brain cells with his device, the more important the work of the speech therapist gets. She asks me to count from 1 to 20 and then backwards, from 20 to 1. She shows me drawings, for example of a comb or a table. I have to name them. Sometimes I hear her say "latency". It usually stands for the time span between a trigger and its reaction. During the operation, however, it means that I take too long to respond or that my answer is not correct. Which shows the surgeon he has to take special care, otherwise I might lose the ability of counting or remembering words.

The word 'latency' will always remind me of the days in the hospital that turned my life into a 'before' and an 'after'.

The team in the theatre manages to remove almost all the tumour cells in the three-hour operation. The sawn out piece is reattached to the skull with titanium screws, the piece of skin sewn on the cutting line. I'm pushed to the intensive care room. I think the stress is over. It's just as well I don't yet know what's still to come.

I want to sleep for a very long time. No chance. A nurse wakes me up every hour to make sure I'm not in a coma and I don't have a haemorrhage. He shines a torch into my eye, I have to tell him my name and my birth date and I have to push my feet against his hands.

I'm starting to feel the pain and I ask the nurse for a stronger medicine. He gives me Vilan, a drug similar to morphine. The effect quickly wears off. I ask for more. The nurse gives it to me. The painkiller loses its once intense effect. Hour after hour the same kind of torment. I just want to get away from here.

Tuesday 4 January 2005. At lunch time I can finally leave intensive care. I don't feel like eating. My jaw hurts. A nurse explains that my chewing muscles were cut in the operating room to have better access to the tumour. Later on a doctor sewed them together.

In the afternoon I'm asleep on the ward. A phone call from the hospital reception wakes me up. My health insurance is refusing to pay for the operation because I had officially left Switzerland. The horrible news pumps adrenaline through my blood. I had made sure before I left that I would remain insured. Even if the catastrophic message is correct, I would rather deal with it later. It turns out to be just a misunderstanding at a bad time.

I fall asleep again. In my dreams I play a videogame against a friend. If you hit the other player on his chest, you steal his force. I beat him forcefully. My opponent, screaming, turns into a creature covered with a shell full of bristles. With a groan, he falls into my arms and breathes his last. I tremble when I wake up.

I realise I might soon be dead. I don't want to think about it too much, I prefer to imagine a happy future with my girlfriend.

Wednesday 5 January 2005. The pressure in my head had been building up in the months before the operation – now it's

gone. It feels as if happiness hormones have been poured into my brain. My body surprises me too. I'm fed up with hospital food, I long for fresh vegetables and pasta cooked *al dente*.

Despite eating double portions, I lose several kilos. And I can't even go to the toilet. Later, a medical expert explains that phenomenon: the operation weakened my body so much that my metabolism just can't get enough nourishment.

A nurse takes the intravenous drip out of my wrist. Finally I can shower again without a plastic bag around my arm.

In the evening, a few friends pass by – in their car. I make my escape for two hours. Putting on jeans feels adventurous. I cover the bandage over my left ear with a woollen hat. We go to a bar full of young people. Despite the heat, I leave my head covered. The skin around my eye is swollen and purple. I look like I have been beaten up. People stare. But I almost jump to the ceiling from the sheer joy of being back in life.

This makes it a particularly hard landing when they tell me the results a couple of days later. The cancer is a glioblastoma multiforme. There is no brain tumour with a faster growth rate. After its removal, a few leftover cells are enough to cause a new outbreak. Life expectancy: on average barely one and a half years. A nurse tells me secretly that patients with this diagnosis are nicknamed "poor bastards" in the clinic.

"Forget about an old age pension," a speech therapist tells me in a shrieking voice, four days after the operation. I just need to relax, but she does an ultra-heavy test with me. She's not satisfied with the results: "A journalist should be smarter." There is a time bomb ticking, she says, and I should think carefully about what to do with the limited amount of time I have left.

The love of my girlfriend more than makes up for such a lack of empathy. But the brain tumour is threatening something fundamental in me. I'm generally brain focused. Journalism is my profession – also a vocation. The cancer is spreading in my speech centre. Providence or coincidence? Shall I take it as a sign, and devote myself to other things?

Despite radiotherapy the tumour is back a few months later. Without treatment, I'm told, the growth will double in size every month. I begin chemotherapy, against my previous convictions. According to my doctor, this is why I'm still here.

The cure is a curse and a blessing. Temozolomide is the name of this drug – it arrived on the market a few years ago. The long-term effects are unknown. I take it in a four-week cycle, swallowing pills for five days and then taking a break for 23 days. I also need constant medication to prevent epileptic fits caused by the tumour.

The immediate reaction to this kill-or-cure remedy is better than might be feared. My appetite, my hair, my sense of balance – it's all here. I soften side-effects with alternative therapies, but despite acupuncture, anthroposophic medicine and Qigong, I feel sick during each pill cycle. My white-blood-cell count falls and I need a sleep during the day. I carry on with chemotherapy. The last few tests have shown good results. My tumour has not disappeared, but it's shrunk. My doctors warn me not to miss even a single chemo cycle, but nobody knows if the tumour will one day become immune to the remedy and carry on growing.

The idea of taking on a job in London is out of my mind. It is better to stay in my home country. I write articles again every now and then. My girlfriend and I are still very happy.

It may sound corny, but I live every day as if it were the last one. Small things make me happy, like the special way sunlight looks on a winter day. At the same time, I behave as if I didn't have to fear an end. For instance I book travel a long time ahead. That way I keep hope alive.

More than three years after his operation, Eric Baumann remains well and has reduced his medication from every 4 weeks to every 8 weeks.

■ This is an abridged version of an article that was first published in *Das Magazin*, the weekend supplement to the Swiss national daily *Tages-Anzeiger*, 23 December 2006

"Nobody knows if the tumour will one day become immune to the remedy and carry on growing"

European Leukemia Network: making fragmentation a thing of the past

Marc Beishon

Efforts to improve the care of Europe's leukaemia patients have been boosted by a highly-motivated, well-focused network that is integrating the work of trial groups and partner groups, involving diagnostics, treatment, registries and guidelines.

While debate about how to fix the fragmented nature of European cancer research continues, there is one group that has been quietly getting on with the job of transnational collaboration. The movers behind the European Leukemia Network ('European LeukemiaNet' or ELN; www.leukemia-net.org), now in its fourth year, have a justifiable claim to be running one of the most far-reaching oncology networks to date. As of January this year it has brought together national leukaemia study groups comprising 147 institutions in 28 countries, more than 1,000 researchers – and potentially tens of thousands of patients.

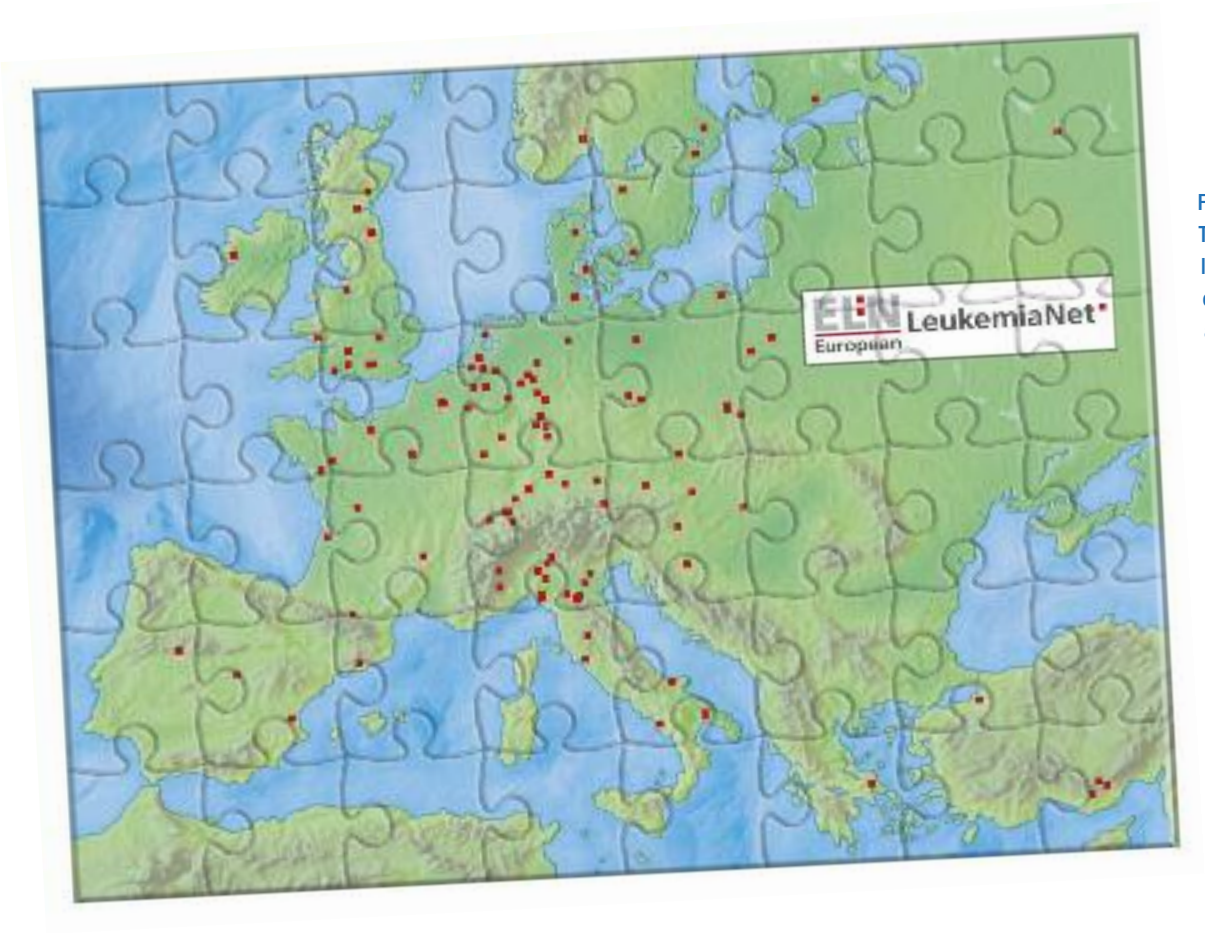
So far, achievements include an annual symposium with a growing attendance, implementation of new treatment guidelines, progress with standardising monitoring techniques and the start of a number of clinical trials and registries for certain leukaemias.

However, the ELN is a product of the European Commission's Sixth Framework Programme and has limited funding – the challenge will be to secure cash to sustain it after the official project end in 2010. The signs are that it may succeed, thanks to partnerships with industry and other funding sources – as evidenced by a tie-up with Novartis for one of the most advanced categories, chronic myeloid leukaemia (CML). Progress so far has been all the more notable because the initial proposal to the EC for a 'network of excellence' was met with only a fraction of the funding asked for – €6 million instead of €30 million.

The ELN is coordinated by Rüdiger Hehlmann, professor of medicine at the Mannheim Medical Faculty of the University of Heidelberg, and a CML expert. It is modelled on a German Competence Network for acute and chronic leukaemias, funded to the tune of almost €12 million since 1999 by the country's Ministry of Research and Education.

The Competence Network – there are two others for cancer in Germany, for lymphomas and paediatric oncology – was formed to address a number of deficiencies in research and care, including incomplete identification of the country's population of leukaemia patients, duplication and fragmentation of clinical trials (and missed opportunities to recruit into trials), and lack of definitions and standards for diagnostics and therapeutic criteria.

As Hehlmann and colleagues wrote in an editorial in *Leukemia* (2004, 18:665–669), the aim of the Competence Network is to support excellence in care and research, and also "incorporate insights from gene array research into clinical practice…and to migrate rapidly to molecular classification of



Fitting the pieces together. The ELN connects 95 leukaemia trial groups covering 147 institutions, and 102 interdisciplinary partner groups involved in diagnostics, treatment, registries and guidelines for six different types of leukaemia across 28 countries, offering an impressive role model for those aiming at a more general integration of Europe's cancer research efforts

leukaemias… The network offers a competitive advantage for participating doctors and scientists from Germany and neighbouring countries." Now, with the ELN, that advantage looks to be spreading to many more countries, and it is just the kind of collaboration for less common tumour types that many senior oncologists feel Europe is uniquely able to exploit.

For the relatively low funding the ELN started with, the programme looks hugely ambitious. In keeping with European Commission parlance, it comprises a number of 'work packages' – 16 in total – with the initial objective of integrating 95 leukaemia trial groups covering all leukaemia types, their 102 interdisciplinary partner groups (involving diagnostics, treatment, registries and guidelines) and industry.

There are six work packages for clinical trials for the disease types – acute lymphoblastic leukaemia (ALL), acute myeloblastic leukaemia (AML), chronic myeloid leukaemia (CML), chronic lymphoblastic leukaemia (CLL), chronic myeloproliferative diseases (CMPD) and myelodysplastic syndromes (MDS). The other packages support interdisciplinary topics such as registries, gene profiling and guidelines. In addition, there is a network management centre and support for communications and information technology.

A CRITICAL MASS

According to Susanne Saussele, a haematologist-oncologist at the University of Heidelberg, and the ELN's scientific network manager, the roots of the project also lie in existing European groups, such as that for CML, but the ELN has widened the number of countries taking

For the relatively low funding the ELN started with, the programme looks hugely ambitious

part. "We have over 20 now for CML, more than double the original number, and the new participants include several from eastern Europe," she says. Indeed, the ELN as a whole also embraces participants from Russia, Turkey and Israel as members.

There has been more long-standing international cooperation generally in rarer cancers because of the need to assemble a critical mass of patients and knowledge, says Saussele. Each disease group operates independently and is a network in its own right. Leadership of the work packages is distributed around Europe, although the core activities, including the network management centre, are based in Germany.

The various leukaemia groups have continued existing trials and started new pan-European ones using common data sets, response criteria and diagnostic standards established by the ELN (although as Saussele comments, the different national interpretations of the European Trials Directive has slowed progress).

There is a strong focus on the diagnostic and treatment side, such as the growing use of molecular monitoring and gene profiling, and a number of therapeutic guidelines have been published. Cooperation with other bodies, such as the European Organisation for the Research and Treatment of Cancer (EORTC) and the European Group for Blood and Marrow Transplantation (EBMT), is ongoing. A European leukaemia registry is an ultimate goal of the ELN, and most registry progress so far has been with CML and MDS.

The CML group has received a major boost with a joint ELN/Novartis European Treatment and Outcome Study (EUTOS). This, as the name suggests, is aimed at improving and standardising treatment of CML in Europe, given the effectiveness of the Novartis 'blockbuster' drug, Glivec (imatinib).

The challenge with CML is to treat it before it enters an acute, often fatal stage, which, without treatment, almost everyone with the disease will progress to. Some 5,000–10,000 people in Europe are diagnosed each year with CML, and about 60,000 are living with the disease.

The dramatic improvement in outcomes for CML came about once the mechanism of the Philadelphia chromosome abnormality was understood, and five-year survival rates have increased to 90% with Glivec's inhibition of the process of leukaemia cell proliferation – up from the 60% achievable with interferon or bone marrow stem cell transplantation. Today, all patients with a major molecular response – eliminating virtually all the tumour cells – are alive after five years.

The challenge now is to raise the bar in treatment standards across Europe, including routine use of PCR (polymerase chain reaction) testing, which is the molecular test for determining whether minute levels of cancer cells remain in the blood, and is more precise than cytogenetic testing from bone marrow or blood samples, which in turn is superior to basic blood analysis.

Building a network of labs that can carry out tests to a reference standard is one of the aims of EUTOS. These tests could include monitoring blood levels of Glivec – not least for adherence with taking this expensive drug. Building a European registry of CML patients is also part of the project. Among other aims, this will help quantify much more accurately just how many cases there really are, and answer patients' questions on outcomes with more certainty. Education for healthcare professionals is another part of EUTOS (as it is for all of the ELN).

EUTOS is also mooted as one of the first genuine cooperations of its type between academia and industry. For Novartis it does of course potentially widen the market for its drug, but it also opens pathways to faster development for new agents, and several other drugs (for example, for patients resistant to Glivec), are also becoming available. But the input from Novartis is substantial – the company is putting €14 million over three years into the ELN.

Saussele stresses that the network is strongly protective of its independence – researchers around Europe will not cooperate without mutual trust, she says. Various other funding sources are being explored, and the ELN is considering establishing a foundation that would accept contributions from industry and other parties.

Certainly, what the ELN has in abundance is open access. A good deal of effort has gone into developing a content management system for its website to allow all the project details – trials, papers, reports, contacts etc – to be easily obtainable. Those not involved in leukaemia may gain useful insight into this model for transnational collaboration, not least from reading the original proposal to the EC.

The challenge now is to raise treatment standards across Europe, including routine use of PCR testing

Outcomes after cisplatin alone or in combination regimens versus hydroxyurea during pelvic irradiation for cervical cancer

Dirk Rades and Steven Schild

Cisplatin-based chemoradiation has been shown to be superior to radiotherapy plus hydroxyurea for stage IB to III cervical cancer, conferring better survival rates with modest long-term toxicity.

Almost 10 years ago, five randomised trials that included almost 1,800 patients demonstrated a survival benefit of 30%–50% for cisplatin-based chemoradiation compared with radiotherapy alone in patients with locally advanced cancer of the cervix. After an initiative of the National Cancer Institute, two to six times more patients in the US received chemoradiation than before the initiative, resulting in improved survival in these patients. Despite these findings, many oncologists are still concerned about the efficacy and toxicity of cisplatin-based chemoradiation.

On the basis of the RTOG-9001 trial, one may question whether cisplatin-based chemoradiation is superior to radiotherapy alone for all stages of disease from IB to IVA.[1] The trial compared pelvic irradiation plus chemotherapy (cisplatin+5-fluorouracil) to irradiation of only the pelvic and para-aortic lymph nodes. The original report published in 1999 demonstrated a significant survival benefit for stage IB/II tumours (n=273), but not for stage III/IVA (n=116) tumours. The results were confirmed in the long-term analysis, which included 228 survivors and had a median follow up of 6.6 years.[2] In comparison with radiotherapy alone, chemoradiation resulted in improved overall survival (41% vs 67% at 8 years; P<0.001), disease-free survival (36% vs 61%; P<0.001), and loco-regional control (65% vs 82%; P<0.001).[2] Grade 3–4 late toxicity was reported as 14% in each group (P=0.50). A subgroup analysis revealed that the benefit of combined therapy was limited to patients with stage IB/II disease (P<0.001 for all end points). For those with stage III/IVA disease, only a trend towards improved outcome was observed (overall survival, P=0.07; disease-free survival, P=0.05; loco-regional control, P=0.065), a result that was most likely attributable to the relatively small number of patients in this subgroup.

The long-term results of the RTOG-9001 trial encouraged Rose et al. to evaluate the long-term results of their trial, GOG-120 (see opposite), particularly because the number of patients with International Federation of Gynecology and Obstetrics (FIGO) stage III tumours enrolled in this trial was comparatively large (n=234, 45%).[3] Indeed, concurrent cisplatin-based chemotherapy was associated with

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significantly improved overall survival (OS) and progression-free survival (PFS) compared with radiotherapy plus hydroxyurea. Both 5-year and 10-year OS rates were increased by 20%. The survival benefit conferred by concurrent cisplatin-based chemotherapy in cervical cancer is much higher than that conferred by adjuvant chemotherapy in patients with breast cancer. Furthermore, the long-term results of the GOG-120 trial demonstrate that the survival benefit is not intermediate but long lasting (at least 10 years), with modest late toxicity (less than 5% grade 3–4 toxicity).

Two of the three other trials (besides RTOG-9001 and GOG-120) that favoured cisplatin-based chemoradiation for locally advanced cervical cancer included only patients with stage IB2, IB or IIA tumours. The third study included stage III/IV tumours, but no stage-related subgroup analyses. The GOG-120 trial is the only study that allows conclusions to be drawn regarding the value of cisplatin-based chemotherapy for stage III cervical cancer.[3] Future investigations will be needed to clarify the potential benefits of newer systemic agents and the role of cisplatin-based chemotherapy for stage IVA disease.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Synopsis

Peter G. Rose, Shamshad Ali, Edwin Watkins et al. (2007) **Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group study.** *J Clin Oncol 25:2804–2810*

Background. The Gynecologic Oncology Group (GOG) protocol was the second of five randomised trials that examined the long-term outcomes associated with simultaneous cisplatin-based chemotherapy and pelvic irradiation for various stages of cervical cancer. Long-term results have been published for the trials.

Objective. To compare the long-term survival rates and toxicities associated with cisplatin-based chemotherapy and pelvic irradiation with those associated with hydroxyurea and concurrent pelvic irradiation in patients with locally advanced cervical cancer.

Design. This randomised phase III study included patients with untreated, stage IIB, stage III or stage IVA invasive squamous, adenosquamous or adenocarcinoma of the cervix. Eligible patients had a GOG performance status of 0, 1, 2 or 3, and normal haematologic, hepatic and renal function with no history of other malignancy. Patients with para-aortic node metastasis, intraperitoneal disease or disease outside the pelvis were not eligible for inclusion.

Intervention. Patients were randomly allocated to one of three chemotherapy regimens: cisplatin (40 mg/m^2 for 4 hours before irradiation on days 1, 8, 15, 22, 29 and 36); combined cisplatin (comprising cisplatin 50 mg/m^2 for 4 hours before irradiation on days 1 and 29, fluorouracil 4 g/m^2 as 96-hour infusions starting on days 1 and 29, and hydroxyurea 2 g/m^2 bi-weekly for 2 hours before radiation on weeks 1–6); or hydroxyurea (3 g/m^2 bi-weekly for 2 hours before radiation on weeks 1–6) alone. All chemotherapy regimens were delivered during external irradiation treatment. Pelvic irradiation was delivered at a dose of 1.7 Gy fractions to all patients, with a total dose of 40.8 Gy being given to patients with stage IIB and 51.0 Gy to patients with stage IIIB/IVA disease.

Outcome measures. The primary outcomes were progression-free survival (PFS) and overall survival (OS). Toxicity was a secondary outcome.

Results. During the period 1992–1997, 575 patients enrolled in the study, of whom 49 were ineligible, leaving a total study population of 526 patients. For surviving patients, the median follow-up time was 106 months. At 30 months' follow-up, PFS rates were 63% for the cisplatin regimen, 63% for the cisplatin-combination regimen and 42% for hydroxyurea alone. The corresponding PFS rates at 60 months and 120 months were 58%, 57% and 35%, and 46%, 43% and 26%, respectively. OS rates at 30 months were 70% in the cisplatin group, 70% in the cisplatin-combination group and 53% in the hydroxyurea group. At 60 months and 120 months, the corresponding rates of OS were 60%, 61% and 40%, and 53%, 53% and 34%, respectively. The relative risks of disease progression or death for the cisplatin regimen and the cisplatin-combination regimen in comparison with the hydroxyurea regimen were 0.57 and 0.51, respectively. In total, 518 patients received radiation. Acute urologic or gastrointestinal toxicities occurred in 66 patients in the cisplatin group (19.1%) and in 29 patients in the hydroxyurea group (16.8%).

Conclusion. Cisplatin-based chemotherapy during pelvic radiation improves long-term OS and PFS of patients with locally advanced cervical cancer, with acceptable acute and late toxicity.

Acknowledgement: The synopsis was written by Mandy Aujla, Associate Editor, *Nature Clinical Practice*.

Are metastatic testicular tumours curable with high-dose chemotherapy and stem-cell rescue?

Giovanni Rosti, Ugo De Giorgi and Paolo Pedrazzoli

A retrospective study has shown that haematopoietic stem cell rescue in tandem with high-dose chemotherapy should be considered a major treatment option in patients with testicular cancer following first-salvage chemotherapy and/or in cisplatin-refractory disease.

Although cisplatin-based chemotherapy cures approximately 80% of patients with newly diagnosed metastatic germ-cell tumours, the outcome in those failing initial chemotherapy is much less favourable and dependent on certain well-defined clinical factors.[1] Primary salvage options in patients who do not respond to first-line chemotherapy include conventional-dose cisplatin-based regimens, while high-dose chemotherapy (HDCT) with haematopoietic stem cell rescue has been actively investigated in the last two decades, with controversial results.[2]

Einhorn and colleagues have retrospectively analysed their experience of tandem HDCT with carboplatin and etoposide in a large series of consecutive men with metastatic testicular cancer that had progressed after receiving cisplatin-containing combination chemotherapy. This study shows 70% and 50% four-year disease-free survival in patients who received HDCT as second-line or third-line or later therapy, respectively. As it is a retrospective review, one may argue that the results are biased by patient selection. This does not seem to be the case, however, as even patients with very poor prognosis achieved long-term disease-free survival – 50% of survivors were classified high-risk by the International Germ Cell Cancer Collaborative Group classification[3] and 45% had platinum-refractory disease. It is important to note that all patients in this series received peripheral-blood progenitors as sources of haematopoietic stem cells. This strategy allowed a rapid engraftment, thereby permitting the administration of two courses of high-dose carboplatin plus etoposide with planned delays at three-week intervals and acceptable toxicity. In addition, peripheral-blood progenitors were enriched for CD34+ haematopoietic cells, a procedure which may have a role in eliminating possible cancer cells from the graft. The source of stem cells and their ex vivo manipulation may well have contributed to the positive results of the study, although there are no evidence-based data to support this hypothesis at present.

Results provided by Einhorn et al. are apparently in contradiction with data from two recently published randomised trials[4,5] that fail to demonstrate a benefit of HDCT over conventional chemotherapy in patients with a poor prognosis, albeit in earlier phases of the disease. Both studies, designed in the early 1990s during an era of great expectations for HDCT, were planned to detect an overoptimistic improvement of event-free survival. The use of bone-marrow stem cells in some patients has resulted in high transplant-related mor-

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Synopsis

Lawrence Einhorn, Stephen Williams, Amy Chamness et al. (2007) **High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors.** *N Engl J Med 357:340–348*

Background. Salvage therapy is used in patients with germ-cell tumours who relapse after initial chemotherapy, and often includes cisplatin combination chemotherapy or high-dose chemotherapy plus autologous haematopoietic stem-cell transplantation to rescue the bone marrow.

Objective. To investigate the efficacy of high-dose chemotherapy (HDCT) and stem-cell infusion as treatment for cisplatin-resistant metastatic testicular cancer.

Design and intervention. In this retrospective study, 184 patients with metastatic testicular cancer who had received HDCT and peripheral-blood stem-cell rescue from February 1996 to December 2004 were reviewed. Peripheral-blood stem cells were collected and purified before commencement of HDCT. Patients who had received first-line high-dose salvage chemotherapy and whose tumour had not progressed within four weeks of previous treatment were given standard doses of vinblastine, iphosphamide and cisplatin before HDCT. Patients who had already received iphosphamide-based salvage chemotherapy were given HDCT only. High-dose chemotherapy comprised two cycles of intravenous carboplatin (700 mg/m^2 of body surface area) plus etoposide (750 mg/m^2 of body surface area) given five, four and three days before the infusion of peripheral-blood stem cells. Following recovery of granulocyte and platelet counts, a second cycle of HDCT was administered.

Outcome measure. The primary outcome measure was duration of disease-free survival.

Results. The median age of patients was 31 years (range 15–58 years). All but 11 of the 184 patients received the second course of HDCT. Over a median follow-up period of 48 months (range 14–118), 116 patients remained disease free. Complete remission was noted in six patients, four after receiving paclitaxel plus gemcitabine, and two after undergoing subsequent resection of a germ-cell tumour. Among the 135 patients who received HDCT plus haematopoietic stem-cell rescue as second-line therapy, 94 were disease-free during follow-up. Of 49 patients who received treatment as third-line or later, 22 were disease-free throughout follow-up. Among the study participants, 40 patients had platinum-refractory disease, of whom 18 were disease-free during follow-up; of the 144 patients with platinum-sensitive cancer, 98 were disease-free at study completion. Approximately 74% of patients with seminoma and 60% of patients with nonseminomatous germ-cell tumours were disease-free throughout follow-up. Three drug-related deaths occurred during treatment.

Conclusion. HDCT plus haematopoietic stem-cell rescue can potentially cure patients with testicular tumours, even when used in platinum-refractory disease or as third-line or later treatment.

Acknowledgement: The synopsis was written by Mandy Aujla, associate editor, *Nature Clinical Practice.*

tality in these studies. Nevertheless, HDCT provided statistically significant benefit in the subgroups of patients with unsatisfactory marker decline during first-line chemotherapy[4] and who achieved complete response with conventional therapy.[5] We believe that, on the basis of the robust data provided by Einhorn and colleagues, a well-designed randomised trial of haematopoietic-stem-cell transplantation and HDCT versus conventional-dose chemotherapy should be performed in patients with poor-prognostic clinical features who relapse after initial chemotherapy.

At present, there should be no debate on the use of tandem-HDCT in patients with germ-cell tumours who have failed second-line therapy.

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NEWSROUND

Selected reports edited by Janet Fricker

Expertise counts in diagnostic ultrasound for ovarian cancer

➜ The Lancet Oncology

Using expert ultrasonographers over regular operators for diagnosing ovarian cancer results in a significant reduction in the overall number of diagnostic procedures required and reduces length of inpatient hospital stays, according to a recent study.

The established way to distinguish benign from malignant tumours in the region of the uterus, ovary or fallopian tubes (known as adnexal tumours) is assessment of structural features (such as wall structure, blood vessels and presence of fluid) using ultrasound. Ultrasonography, however, is subject to substantial interobserver variability, with experienced operators being significantly more accurate in their diagnosis than the less experienced.

The study set out to assess whether the level of operator skill had a measurable impact on patient management. Overall, 150 patients with suspected ovarian cancer, referred to the regional gynaecological cancer centre at Guy's and St Thomas' NHS Foundation, London, between 3 May 2004 and 15 February 2007, were randomised to level III (expert) ultrasonography (n=77) or level II (routine) ultrasonography (n=73). Level III ultrasonography was undertaken by gynaecologists with a special interest in gynaecological ultrasound who had more than 10 years' experience in the procedure; while level II ultrasonography was undertaken by ultrasonographers trained in gynaecological ultrasonography. For all patients, both transvaginal and transabdominal scans were undertaken to ensure complete assessment of the entire abdominal cavity.

Results showed the number of major surgical staging procedures for presumed ovarian cancer undertaken in women screened by level III ultrasonography was 17 of 77 (22%), compared with 27 of 73 (37%) for those screened by level II ultrasonography (P=0.049). There was also a reduction in follow-up procedures after expert sonography, with the median number of follow-up scans being two (range 0–5) in the level II group, compared with one (0–4) in the level III group (P=0.0004). "This finding is likely to be the consequence of the greatly increased proportion of patients in whom a conclusive diagnosis of the nature of the adnexal tumour was possible from level III ultrasonography compared with level II ultrasonography," write the authors.

Furthermore, results showed that a histological diagnosis was provided to clinicians for 76 of 77 patients (99%) in the level III group compared with only 38 out of 73 patients (52%) in the level II group (P<0.0001). The total number of surgical procedures was similar in the two groups – 35 of 73 (48%) in the level II group versus 33 of 77 (43%) in the level III group (P=0.53). However, the number of minimally invasive procedures was higher for the level III group than the level II group. This, write the authors, is likely to have contributed to the significant decrease in the median duration of hospital stay for patients in the expert level III group (5 days; range 1–9 vs 6 days; range 3–13).

The authors add that the effect of expert scanning might have been even greater if it had been used in the primary assessment of ovarian pathology. "Increased confidence in the diagnosis of benign ovarian lesions is likely to decrease the need for additional diagnostic tests, such as MRI or serum CA-125 concentration, and also decreases the number of referrals to regional cancer centres," they write.

■ Effect of quality of gynaecological ultrasonography on management of patients with suspected ovarian cancer: a randomised controlled trial. J Yazbek, SK Raju, J Ben-Nagi et al. *Lancet Oncol* February 2008, 9:124–131

PET scans are better than CT for measuring sarcoma response

➜ Clinical Cancer Research

Positron emission tomography (PET) – a type of scanning that assesses the activity of cells in the body – is much more sensitive and more accurate than conventional imaging methods in detecting responses to treatment in patients with sarcoma, according to one of the first studies to look at this issue.

The study compared PET scanning with CT in 42 patients with high-grade soft tissue sarcomas. Scans were taken before and after the patients were treated with chemotherapy, prior to surgery to remove their tumours. The researchers measured the metabolic or chemical activity of

the tumour cells using a specific PET probe that assesses glucose metabolism. This allowed them to determine whether the cancer cells were still alive and dividing after treatment. After removing the tumours during surgery, they analysed the cells directly to assess whether chemotherapy had affected their activity.

Assessing the effects of chemotherapy in people with sarcomas has previously been difficult, because the standard measure for response to cancer treatment – Response Evaluation Criteria in Solid Tumors (RECIST) – has proved unreliable in these cancers. Using this method, patients are scanned by CT or MRI to assess whether a tumour has shrunk in response to treatment. Previous research has shown that treatment may change the activity of sarcoma tumour cells in a way that improves a patient's survival, even though a change in tumour size is not apparent using RECIST criteria. This has important implications for patients, because they may be taken off a treatment that is potentially improving their prognosis, because their tumour is not shrinking.

"We knew from our experience with neoadjuvant therapy in sarcoma patients that measuring tumour size correlated poorly with response," explained Fritz Eilber, director of the Sarcoma Program at the Jonsson Comprehensive Cancer Center at the University of California at Los Angeles, and one of the authors of the new study. "We have removed many tumours that have not changed in size with treatment, or have even grown, but are completely dead on pathologic analysis. Just because the tumour doesn't shrink doesn't mean the treatment didn't work," he added.

Results from the study showed that PET scanning was much more accurate in detecting response to chemotherapy in sarcomas than conventional scanning. PET scanning identified all of the patients whose tumour cells responded to treatment. In contrast, using standard tumour-size based criteria (RECIST) identified only one in four patients (25%) whose tumour cells had responded.

The study findings have important implications, say the researchers. "PET should be used to monitor treatment response in patients with high-grade soft tissue sarcomas," they conclude.

■ Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. V Evilevitch, WA Weber, WD Tap et al. *Clin Cancer Res* 1 February 2008, 14:715–720

Minimally invasive staging procedure works in lung cancer

➔ JAMA

An evaluation of several methods of endoscopic biopsy suggests a minimally invasive approach can accurately stage suspected lung cancer. A combined approach using two different endoscopic procedures has been shown to provide the most accurate method of diagnosis.

Accurate staging of lung cancer is recognised as critical for the selection of optimal therapy. Patients without evidence of mediastinal lymph node metastases are generally offered surgical resection, whereas those with metastases are treated with chemoradiotherapy (with or without surgery).

Noninvasive staging with chest CT or PET has been associated with high rates of false-positive and false-negative results. The American College of Chest Physicians therefore recommends invasive staging of the metastatic mediastinal lymph nodes, a surgical procedure requiring general anaesthesia that carries a 2% risk of major morbidity.

More recently, less invasive methods have emerged, including blind transbronchial needle aspiration, endobronchial ultrasound-guided fine-needle aspiration, and transoesophageal endoscopic ultrasound-guided fine-needle aspiration.

In the *JAMA* study, Michael Wallace and colleagues, from the Mayo Clinic College of Medicine in Florida, compared the diagnostic accuracy of each of these endoscopic staging procedures. The study involved 138 suspected lung cancer cases seen consecutively between November 2004 and October 2006, with each patient undergoing the three procedures sequentially in a single combined procedure. Pathologic confirmation and clinical follow-up took place at 6–12 months.

Results showed that 42 patients (30%) had malignant lymph nodes. The endobronchial ultrasound-guided aspiration method was more sensitive than the blind transbronchial procedure, detecting 29 (69%) versus 15 (36%) of the 42 malignant lymph nodes (P=0.003). Transoesophageal aspiration also detected 29. Combining the ultrasound-guided endobronchial and the transoesophageal endoscopic procedures detected 10 more malignant nodes than either method used alone.

If mediastinoscopy had been performed only when the results of the endobronchial and transoesophageal endoscopic procedures were negative, write the authors, an invasive procedure could have been avoided in 28% of patients (39/138).

"If these data are confirmed by other studies, they thus suggest that endoscopic ultrasound-guided fine-needle aspiration plus endobronchial ultrasound-guided fine-needle aspiration… may be an alternative method for surgical staging of the mediastinum in patients with suspected lung cancer," they conclude.

■ Minimally invasive endoscopic staging of suspected lung cancer. M Wallace, JMS Pascual, M Raimondo et al. *JAMA* 6 February 2008, 299:540–546

Ki-67 does not predict response to adjuvant breast cancer treatment

➔ Journal of the National Cancer Institute

In breast cancer, having a high percentage of tumour cells expressing the proliferation antigen Ki-67 – a high tumour Ki-67 labelling index – has been found to be associated with poor disease-free survival but, according to a retrospective analysis, it does not predict response to adjuvant treatment.

Expression of the Ki-67 antigen indicates cells in the active phase of the cycle. Several small studies have reported that a high Ki-67 labelling index predicts better response to neoadjuvant chemotherapy.

To investigate whether the Ki-67 labelling index could also be used to predict response to adjuvant chemoendocrine therapy, Giuseppe Viale

and colleagues from the European Institute of Oncology, Milan, undertook a retrospective assessment of Ki-67 expression in tumour samples from the International Breast Cancer Study Group trials VIII and IX. The two large randomised trials, conducted between 1988 and 1999, compared endocrine therapy alone versus CMF chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) followed by endocrine therapy among pre/perimenopausal (trial VIII) and postmenopausal (trial IX) breast cancer patients with node-negative, hormone-receptor-positive disease.

The team assessed 1,924 formalin-fixed paraffin-embedded samples for Ki-67 labelling index, using the mouse monoclonal antibody MIB-1. They found Ki-67 levels could not be used to predict which patients benefited from the addition of chemotherapy to endocrine therapy in the adjuvant setting. Results did show, however, that a high Ki-67 labelling index was associated with a worse disease-free survival among both postmenopausal women (trial IX; recurrence or death HR 1.60, 95% CI 1.26–2.03, $P<0.001$) and pre/perimenopausal women (trial VIII; HR 1.66, 95% CI 1.20–2.29, $P=0.002$).

Other biomarkers are needed to define which women with endocrine-responsive node-negative early breast cancer benefit from the addition of adjuvant chemotherapy to endocrine therapy, the authors conclude.

In an accompanying editorial, Matthew Ellis from Washington University, St Louis, Missouri, wrote, "This result is striking because it indicates that patients with aggressive node-negative hormone-receptor-positive breast tumours who have a high growth fraction – the patients most in need of additional therapy – obtain no extra benefit from the addition of cyclophosphamide, methotrexate, and 5-fluorouracil to their endocrine regimen."

■ Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. G Viale, MM Regan, MG Mastropasqua et al, on behalf of the International Breast Cancer Study Group. *J Natl Cancer Inst* 6 February 2008, 100:207–212

■ Improving outcomes for patients with hormone receptor–positive breast cancer: back to the drawing board [editorial]. MJ Ellis. *ibid* pp159–161

Sorafenib patients require monitoring for hypertension

→ The Lancet Oncology

Patients taking sorafenib (Nexavar) need close monitoring and treatment for high blood pressure to prevent cardiovascular complications, according to a recent study.

Sorafenib is a multikinase inhibitor used to extend survival in patients with advanced renal cell cancer (RCC) and hepatocellular cancer. Hypertension has been noted in trials, with an incidence ranging from 16% to more than 42%. Other angiogenesis inhibitors, including bevacizumab (Avastin) and sunitinib (Sutent), have also been associated with hypertension.

With the aim of understanding the overall risk for hypertension in patients on sorafenib, Shenhong Wu and colleagues from The University of New York conducted a systematic review and a meta-analysis using databases including MEDLINE, the Web of Science and abstracts presented at ASCO meetings. Overall the team identified nine studies, including a total of 4,599 patients with RCC or other solid tumours meeting the criteria of patients being assigned single-drug sorafenib at 400 mg twice daily, with data on hypertension available.

Results showed that the incidence of all-grade hypertension was 23.4% in patients receiving sorafenib, with a 5.7% incidence of high-grade hypertension. Sorafenib treatment was associated with a six-fold increased risk of developing all-grade hypertension compared with controls.

Initially the authors had speculated that RCC would be associated with a greater risk of hypertension than non-RCC malignancies, on account of previous nephrectomy and renal dysfunction. This, however, was not found to be the case. "A possible explanation… is that the increase in blood pressure and hypertension induced by sorafenib is so prominent that the risk associated with RCC is not evident in this setting," write the authors.

Early detection and effective management of hypertension might allow for safer use of sorafenib, conclude the authors. "The hypertensive and cardiovascular side effects of sorafenib need thorough post-marketing surveillance and reporting, and future studies will be needed to identify the mechanism and appropriate treatment of sorafenib-induced hypertension," they add.

■ Incidence and risk of hypertension with sorafenib in patients with cancer: a systematic review and meta-analysis. S Wu, J J Chen, A Kudelka et al. *Lancet Oncol* February 2008, 9:117–123

Androgen suppression therapy does not benefit patients with comorbidity

→ JAMA

Adding androgen suppression therapy (AST) to external radiation treatment increases overall survival in men with high-risk locally advanced prostate cancer, but, according to a recent study, the benefits are not seen in patients with comorbidities.

Several randomised trials have documented increased survival when AST is combined with external beam radiation therapy (RT), compared to RT alone, in localised and locally advanced prostate cancer. As a result, combination treatment has become the standard of care. However, pooled analyses of randomised studies suggest that, in older men, AST administration can be associated with an increased risk of cardiovascular events.

Anthony D'Amico and colleagues from Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, Massachusetts, set out to investigate whether survival benefits in men undergoing AST in combination with RT varied according to their comorbidity illness profiles.

In all, 206 men (median age 72.5 years) with clinically localised or locally advanced non-metastatic prostate cancer and at least one unfavourable prognostic factor were randomised to treatment with RT or RT plus AST. Each patient was assigned a baseline comorbidity score, graded on a scale of 0 (none) to 3 (severe).

After a median follow-up period of 7.6 years, results showed a significant increase in the risk of all-cause mortality in patients receiving RT alone compared with the group receiving both RT and AST (44 vs 30 deaths, HR 1.8, 95% CI 1.1–2.9, $P=0.01$).

When a subgroup analysis was undertaken, the

increased risk in all-cause mortality for men receiving RT alone applied only to those with no or minimal comorbidity (31 vs 11 deaths, HR 4.2, 95% CI 2.1-8.5, *P*=0.001). Among men with moderate or severe comorbidity, 13 of those randomised to RT alone died, compared with 10 randomised to RT plus AST (HR 0.54, 95% CI 0.27–1.10, *P*=0.08).

"The clinical significance of this finding is that preexisting comorbid illness may increase the negative effects of specific anticancer treatments such as AST," conclude the authors. "Therefore, future randomised studies evaluating the impact on survival of adding novel therapies to the current standards of practice in men with clinically localised or locally advanced non-metastatic prostate cancer should consider a pre-randomisation stratification by comorbidity score."

■ Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. AV D'Amico, MH Chen, AA Renshaw et al. *JAMA* 23 January 2008, 299:289–295

The breast cancer personality is laid to rest

→ Journal of the National Cancer Institute

Studies in the 1980s suggested that women who had difficulty expressing emotions might be more prone to breast cancer. However, a recent 13-year follow-up study looking at breast cancer incidence and personality traits has found no evidence of any association.

The study was conducted by Eveline Bleiker and colleagues, from the Netherlands Cancer Institute in Amsterdam. It followed an earlier study by Bleiker, conducted in 1996, which had found a weak association between breast cancer and a high score on the 'anti-emotionality scale' (indicating an absence of emotional behaviour or a lack of trust in one's own feelings). One limitation of that study, reported by the authors, was that follow-up was for a maximum of five years after the psychological assessment, so the assessment could have been detecting the sub-clinical effects of tumour growth.

In the current study, involving the same cohort of women, Bleiker and colleagues followed, for 13 years, 9,705 women attending a population surveillance programme in the Dutch city of Nijmegen between 1 January 1989 and 31 December 1990. All the women were asked to complete a personality questionnaire assessing anxiety, anger, depression, rationality, anti-emotionality, understanding, optimism, social support, 'emotional expression in' (feelings held in or suppressed), 'emotional expression out' (feelings directed toward other people or subjects) and emotional control (control of outward expression of feelings). Information on medical risk factors, like having a first-degree relative with breast cancer, was also collected.

A total of 217 women subsequently developed breast cancer, between 17 May 1995 and 1 January 2003. When their personality profiles were compared with 868 age-matched controls, none of the personality factors examined showed any significant association with increased risk of breast cancer – a result, say the authors, that may help reassure some patients.

"Our finding that no psychological risk profile was associated with the incidence of breast cancer may help oncologists to reassure patients that their personality appears to have played no role in the development of their breast cancer," they conclude.

■ Personality factors and breast cancer risk: a 13-year follow-up. E Bleiker, J Hendriks, J Otten et al. *J Natl Cancer Inst* 6 February 2008, 100:213–218

Oxygen does not help cancer patients with dyspnoea

→ British Journal of Cancer

Use of oxygen therapy fails to improve symptoms of dyspnoea in cancer patients, according to a systematic review and meta-analysis.

Dyspnoea, defined by the American Thoracic Society as a "subjective experience of breathing discomfort", is experienced by 50%–70% of patients with advanced cancer. The use of oxygen therapy is widespread, despite there being little evidence that it works. Treatment should not be undertaken lightly, since the patient's quality of life can be limited as a result of functional restrictions; psychological distress can arise from being reliant on a machine, and use of nasal cannulae can increase the risk of nose bleeds. Furthermore, home oxygen is expensive, with many patients forced to fund treatment themselves.

In an attempt to improve understanding of the use of palliative oxygen, Hope Uronis and colleagues from Duke University Medical Center in Durham, North Carolina, undertook a systematic review in MEDLINE and EMBASE of studies published between 1966 and December 2006. Altogether the team identified four blinded, randomised, crossover trials of cancer patients treated with non-invasive oxygen (nasal cannula, mouthpiece or face mask), where direct comparisons could be made between oxygen therapy and medical air (used as a placebo).

In the studies, dyspnoea ratings were measured using the modified Borg 0–10 numerical rating scale (NRS) or a 100-mm or 300-mm visual analogue scale (VAS). These were converted into standardised mean differences (SMDs). Altogether 134 patients were included in the meta-analysis.

Results showed that oxygen failed to improve dyspnoea in mildly or non-hypoxaemic cancer patients (SMD -0.09; 95% CI -0.22–0.04; *P*=0.16). This, say the authors, translates to a 0.22-point reduction in dyspnoea on a 0–10 numerical rating scale. Most clinicians would consider a 1-point reduction on a 0–10 NRS to be clinically significant.

Patient preferences were also studied, because dyspnoea is subjective and patients often have difficulty describing the sensation – and it is also known that not all patients who benefit from oxygen want to receive it.

Two of the four studies demonstrated statistically significant patient preferences for oxygen. "The data… suggest that there is a population of patients who experience less dyspnoea while receiving oxygen as compared with medical air," write the authors, adding that further research is needed to identify this subgroup. Until that time, decisions regarding palliative oxygen should be made on an individual basis.

■ Oxygen for relief of dyspnoea in mildly or non-hypoxaemic patients with cancer: a systematic review and meta-analysis. H Uronis, D Currow, D McCrory et al. *Br J Cancer* 22 January 2008, 98:294–299

Protection of employment rights: still work in progress

Peter McIntyre

Despite an EU directive outlawing job discrimination, cancer patients are still routinely forced out of work by employers who don't want them or refuse to accommodate their need for lighter work or a shorter working day. Changing attitudes and improving the information and support available to patients will be key to turning the letter of the law into reality at work.

Women with early breast cancer in Quebec, Canada, lose more than a quarter of their income in the year following diagnosis. A study published in the *Journal of the National Cancer Institute* (26 February 2008) shows that women who had jobs when they were diagnosed lose 27% of their income, on average, even when sickness benefits and other forms of compensation are taken into account. One in ten women lose more than two-thirds of their income.

The most severe impact is felt by women who are less educated, live further from the hospital where they are treated, and have more serious disease and less social support. The Laval University team, which conducted the study, concluded, "wage losses resulting from breast cancer can substantially and negatively affect the financial situation of working women and their families."

In both North America and Europe improved treatment of cancer and greater public understanding has helped drive a trend for younger cancer patients to return to work. Barbara Hoffman in her 2005 paper Cancer Survivors at Work: a Generation of Progress (*CA Cancer J Clin* 2005; 55:271–280), reported that in North America more than 70% of cancer survivors of working age returned to work within a year of diagnosis, and more than 80% did so within four years. Young breast cancer survivors had the same employment rates five years after diagnosis as they did at the time of diagnosis.

Yet nearly half of supervisors admitted that they would be less likely to hire someone who had had a cancer diagnosis. Hoffman concluded that, "from the time of diagnosis, survivors need team-based, long-term support in managing their employment opportunities."

In Europe, there are no data on how many cancer patients return to work and how easy they find it to do so. In many European countries, employers still discriminate against people who have had a cancer diagnosis, and patients often come under pressure to resign their posts, or are sacked.

The European Employment Framework Directive, which came into effect in 2004, obliged EU Member States to introduce legislation to outlaw unreasonable discrimination against people with disabilities. The way this legislation has been implemented across the EU varies widely.

JANINE WIEDEL / ALAMY

Legal loophole. Cancer patients are often not up to working as hard as they did when they were healthy, yet many countries do not count them as 'disabled' for purposes of job protection

THE LAW

In the Nordic countries, the Netherlands and the UK, for example, people with long-term illnesses such as cancer are specifically included in the definition of disability, and are therefore protected. Other countries define disability much more narrowly.

The Brussels-based European Disability Forum recently presented the European Commission with a 1.2 million signature petition calling for stronger anti-discrimination legislation. Policy officer Javier Güemes says that better guidance is needed for countries to ensure that people with long-term illnesses are not left out.

"In the European Union we have many realities. We have some countries, like Sweden and Denmark, where it is completely accepted that a person with a chronic illness is a person with a disability. You have other countries where it is still very difficult to convince the disability movement and the public authorities to accept that.

"In Hungary, 5% of the population is considered

WHAT THE DIRECTIVE SAYS

The Council of the European Union approved a Directive on Equal Treatment in Employment in November 2000 to establish a framework to combat discrimination on grounds of religion or belief, disability, age or sexual orientation.

The Directive affirms the importance of giving specific attention to recruitment, retention, training and lifelong learning for people with disabilities. Employers are required to take effective and practical measures to adapt premises and equipment, patterns of working time, distribution of tasks or training.

However, the Directive is silent on whether someone with a long-term illness, such as cancer, is considered in the same category as someone with a disability. The Directive does not protect someone who is "not competent, capable and available to perform the essential functions".

Adaptive measures must not cause the employer a disproportionate burden, taking into account the scale and financial resources of the employer and the availability of public funds. Member States were given a final deadline of December 2006 to comply and must report to the European Commission every five years.

For more about the Directive see: http://europa.eu./scadplus/leg/en/cha/c10823.htm

PHOTOGALLERY asbl FOR EDF

Turning law into reality. The European Disability Forum (www.edf-feph.org) wants anti-discrimination legislation to be backed by concrete measures, targets and objectives, at regional, national and European levels. Last November, they presented Margot Wallström, vice-president of the European Commission, with a 1.2 million signature petition calling for more effective protection for disabled people's rights

disabled, and in Poland it is close to 6% or 7%. When you go to the Nordic countries, 23% are considered to have disabilities. It makes no sense. Maybe between these extremes we can find equilibrium. The European Commission is quite reluctant to take any action because this is an issue of national competence, but they should provide some kind of guidance that can be used by national governments."

Nowhere is the need to clarify anti-discrimination legislation greater than in the field of employment. Under the Directive, employers are supposed to make a 'reasonable accommodation' to adapt the working environment to the needs of people with disabilities, but this may not take into account the needs of people living with cancer.

Güemes says, "Maybe an employer just thinks about ramps for access, or a table for a person in a wheelchair, or a speech reader for a blind person. But when we are talking about people with chronic illnesses, people with chronic fatigue or with mental health problems, then we have to think about reasonable adjustments in another way, such as the time that people can work."

The need for clearer guidance has been made more urgent by a 2006 ruling from the European Court of Justice over the dismissal of a Spanish woman from her work. Chacon Navas was sacked after being away from work ill for eight months. The Spanish courts asked for a ruling to see whether she was covered by the European Directive.

The European Court defined a disability as "A limitation which results in particular from physical, mental or psychological impairments and which hinders the participation of the person concerned in professional life." It said that for a limitation to count as a disability it must be probable that it would last a long time, but also ruled that, for the purposes of the Directive, disability is different from sickness. There was nothing in the Directive to suggest that workers are protected as soon as they develop a sickness.

Chacon Navas lost her appeal, but the European Court has not settled the issue. Her illness was not specified in the court hearings and it was not clear whether she would ever have been able to return to work. The Court did not therefore address the question of whether someone who suffers long-term

"We have to think about 'reasonable adjustments' in another way, such as the time that people can work"

"Good information on patients' rights is the first tool for defending one's right to remain active in society"

impairment because of cancer or other chronic illness, but who can still work, should be given protection.

Some countries have already taken this step. In Italy, the 2003 'Biagi law' includes a specific right for cancer patients to switch to part-time work during or following treatment, and to switch back later to full time work. In 2006, a campaign by the Federation of Italian Cancer Patients' Associations (FAVO) led to a rapid improvement in the temporary disability certificate process, reducing delays from about 12 months to 15 days. This gives patients access to many benefits more rapidly.

Elisabetta Iannelli, a lawyer and a cancer patient since the age of 24, is currently vice-president of the Italian Association of Cancer Patients (AIMaC) and secretary of FAVO. She believes that patients who are able to work should be encouraged to do so. "It is of utmost importance for their quality of life so they can feel an active part of their society."

So far, no data have been collected on the impact of the Italian changes, but the national social security agency INPS has agreed to send out AIMaC leaflets spelling out the new rights. Iannelli says, "We strongly believe that correct information on the patients' rights is fundamental for the quality of life of the patient and his/her family, and is the first tool towards defending one's right to maintain an active role in society."

In the UK, the Disability Discrimination Act was extended in December 2005 to include people with long-term illness such as HIV or cancer. Employers are expected to make 'reasonable adjustments' to help people stay in work, for example, by altering working hours so that someone whose medication affects them in the morning can start work later in the day, and by allowing home working during a period of rehabilitation, and absence from work for rehabilitation, assessment or treatment.

The reality

However, good legislation does not guarantee good practice. In the eight months that followed the extension of the law to people with chronic illness, the Disability Rights Commission took 174 calls from workers with cancer who were experiencing discrimination at work. Most were about a failure to adjust working patterns, but there were also cases of overt discrimination. A woman who worked for a major high street retailer was dismissed when she could not give a firm return to work date following radiotherapy. A care assistant about to return to work following cancer treatment was asked to resign and then dismissed. A woman who had worked for a security firm for 19 years was told she was a 'bad investment' when she asked for time off for reconstructive surgery.

Nicola Pazdzierska, who works for the newly created Equality and Human Rights Commission in the UK, said, "There is good practice out there, but some people with cancer are still being treated appallingly. This happens when people are at their most vulnerable and a lot of employers are not aware of their obligations under the law. Employers have to make reasonable adjustments to help people with cancer to stay in work."

Countries of the 'new Europe' have actually lost some protection, since under the former system jobs were generally protected, even during long-term sickness.

Sanja Rozman has a unique insight into the strengths and weaknesses of protection for people with cancer and other long-term illnesses. As a doctor at the Institute for Rehabilitation in Ljubljana, Slovenia, she assesses how the demands of the workplace will impact on a patient, and how they can be modified. She herself was diagnosed with breast cancer at the age of 46, when she was a working mother with a four-year-old child.

She says that, despite strong formal protection in Slovenia, legal protection is often not enough, especially for workers on short-term contracts. "I encounter every day patients who report on discrimination, subtle and direct psychological pressure. For a survivor in a psychologically vulnerable position these pressures are a real threat."

She says that whether patients want to return to

"There are a lot of women for whom work is not an option, it is the only way they can survive"

work depends on the severity of the disease and on personal circumstances. "It depends not only on the type of illness or the type of job, it also depends on whether you have a big family or other interests in life or whether the job is your prime source of self-esteem. This experience of cancer shakes your value system – you have to reassess which is more important, your health and family or doing the job you like."

In her own case, Rozman returned to work part time ten months after surgery, working four hours a day and no longer doing hospital night shifts. "I am a doctor and this is a vocation, not something you do because you have nothing else to do. For me the job is very important, but I would not die for it. I have had to learn to work more efficiently. I was aware I must not exhaust myself. I must work up to my limit and not past it."

Rozman is on the board of Europa Donna, the European Breast Cancer Coalition, and its Slovenian affiliate. She notices differences in attitudes to work and protection, depending on the status of the women affected.

"The women I meet at a European level are mostly middle-class women who are well-off with a high level of education. Often when I speak with colleagues in western Europe about work, they see themselves sitting in an office speaking nicely with nice people. They don't have any idea of what it is to work in a factory 9–10 hours a day, to be physically active when in pain and ill and in an environment that is hazardous.

"On the other hand, I am in touch every day in my clinic with patients who have done physical work for 40 years and still have to do difficult physical work. They consider it a privilege to be protected and transferred to a lighter job. There are a lot of these women, especially in eastern Europe, who have to support their family. For them, work is not an option, it is the only way they can survive."

Corina Alexandru, President of the Associatia Oncologic Rom, the Romanian Association of Cancer Patients, often meets employers to sort out problems when cancer patients are denied the right to return to work.

"The law is upside down in Romania. Normally, the company has to keep your place open for you, but the law also says that if the company needs someone to do your work when you cannot, they can hire someone else. Cancer patients may have worked for many years in the same company. We do not get cancer because we want it! It is not our fault, and when we have paid for medical insurance then the company has to keep our place until we are able to work again."

Daniel Alexandra was diagnosed with osteoblastoma in his hand at the age of 21. He had a medical certificate and should have been legally protected. But after a year and half, the harbour company where he worked as a driver fired him. He is now having treatment in Spain. "When he comes back to Romania we will have to help him find a job. There are many people like this. After they have finished treatment the company won't accept them back to work – they say they have taken on other employees and don't have any places at the moment."

Alexandru was not able to return to work after her own cancer treatment began eight years ago, but she was able to get a medical pension. The Associatia Oncologic Rom helps survivors to stay active and learn new skills. Alexandru herself has learned to work in stained glass.

Bulgaria, another recently joined EU country, also has good protection under law, with cancer classified as a 'temporary disability' for up to five years from diagnosis, and a board to help employees keep their jobs. But Evgeniya Adarska, who founded what has become the main cancer patient group in Bulgaria, APOZ, says that employers know how to lay off cancer patients without violating the rules.

"A young woman, working in the Bulgarian office of a big international company, was diagnosed with breast cancer. She underwent an operation, had chemotherapy, radiotherapy and hormone therapy, and even before the treatment was over she returned to her office, happy to have a new chance for a life and her own job, far away from the hospitals. But two months after her return, her employment was terminated without notice.

"The end of her contract was a very good excuse to get rid of an employee with an unclear health future. The young woman was heartbroken. The lawyer she talked with did not give her much hope, so she was unemployed only two months after the cancer ordeal. That young woman was me in 2000, the year I decided to set up my first anticancer organisation."

Since then, APOZ has helped many people facing discrimination. Adarska cites a campaign to help two women cancer survivors with excellent work records, who were twice threatened with dismissal. Once APOZ intervened directly and the second time, in 2007, it called on the trade union for support, and on both occasions the jobs were saved. "The two women still work for that company. In 2007, cancer patients in Bulgaria are much stronger and able to fight for their human patient rights. It's extremely important that every patient has the right to choose his or her future life after treatment. I believe that nobody deserves to be harassed because of health problems.

"It is obvious that the law itself is not the only means to help cancer patients, especially in Bulgaria, where going to the court in some cases can be just a waste of time. We are still in the situation where we need to campaign heavily."

There have also been some very positive experiences in Europe. In Finland, Mikael Jungner, was diagnosed with prostate cancer in early 2005 at the age of 40, just as he was about to take up a new post as director-general of the Finnish Broadcasting Company, YLE. The board gave Jungner its full support, and it was not regarded as a big deal for a top executive to be treated for cancer and to carry on working.

Progress. Lawyer and cancer survivor Elisabetta Iannelli helped secure legislative changes that give Italian cancer patients the right to switch to working part time

It may be a long time before this positive experience is translated into the same support and rights for men and women throughout the EU – especially for cancer survivors who work in less glamorous fields.

Javier Güemes from the European Disability Forum says that Europe has to focus on the social barriers that stop people with many conditions playing a full part in life. "Things are changing, but we are far from a perfect situation, that's for sure, and we have to continue fighting. There are wonderful laws, not just in the UK but in Spain, Italy and France etc, but the problem is that the laws are not respected and people with disabilities are not informed of their rights.

"Changing legislation is the first step. Now we have to change the minds, and have to change society to accommodate this new philosophy regarding people with disabilities and people with chronic illnesses. This will take time but I think that things are improving."

"There are wonderful laws... the problem is that the laws are not respected"