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Alex Eggermont

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Direttore responsabile
Emanuele Bevilacqua

All enquiries about *Cancer World* should be made to:
ESO Editorial Office
Viale Beatrice D'Este 37
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e-mail: magazine@esoncology.org
Fax: +39 02 4335 9640

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Our partnership with patients

Heinz Ludwig ■ GUEST EDITOR

Receiving a cancer diagnosis changes everything in your life. It brings fear and uncertainty, it impacts on your body and soul, it affects your partner, family and friends, it has financial implications, it can even change your spiritual outlook. Making considered and informed decisions at a time like this is terribly hard. It's a bit like emigrating to a new country – you don't understand the language, you don't know how things are done, you feel lost and vulnerable, but you have to find a way to settle in and build a new life.

Cancer patients need doctors who can help them in their efforts to come to terms with their diagnosis, and equip them to take informed decisions on treatment options. But doctors cannot do this without developing their own understanding of what patients are going through and how best to respond to needs and wishes that are likely to vary from patient to patient. It is a question of working in partnership.

The European Society for Medical Oncology (ESMO) sees strengthening the patient-physician partnership as a priority. Two years ago, in Nice, we became the first European oncology body to organise a seminar for patients and their families at our annual meeting. In 2003, the second patients' seminar was organised, with patients helping to set the agenda and taking their place on the platform.

In recognition of the growing level of organisation among patients, this year's seminar, scheduled for October 30-31 at the ESMO conference in Vienna, has been organised in collaboration with a number of patient groups, including the European Cancer Patient Coalition (ECPC). Questions of how to strengthen patients' physical, mental and spiritual energy to help them deal with the problems they face will be among the topics up for discussion.

Building an understanding of patients' needs plays a vital role in improving the care we can offer. But seminars like these are also important in the wider battle to improve cancer care. By bringing together patients from all over Europe, they assist the ECPC and other patient groups who are trying to create networks of patient advocates to campaign for improved care and raise awareness of the needs of cancer patients – in their home lives, working lives and social lives. Europe has ten million people directly affected by cancer, and more than ten times that number affected indirectly. Together, we surely represent a potent force for change.

I hope to see you in Vienna.

Heinz Ludwig is a past President of ESMO and Chairman of the ESMO Foundation

Lex Eggermont: a rare hybrid

Marc Beishon

Clinical cancer research is nowadays dominated by medical oncologists, so the election last year of a surgeon to head up the EORTC might seem an unusual choice. But then Alexander Eggermont is an unusual man, whose pioneering work, with TNF in particular, has shown that great things can be achieved by combining surgical and biological know-how.

Of all the top cancer specialists, it would be hard to find one who is juggling as many professional duties as Alexander Eggermont ('Lex' to friends and colleagues), head of surgical oncology at the Erasmus University Medical Centre in Rotterdam. An analogy with the great port city is apt – Eggermont ships himself to an extraordinary number of meetings and conferences each year, even on occasion flying to and from New York in one day.

That doesn't sound much fun – but enjoyment of what he does is a constant theme in Eggermont's career, from early days playing in a blue grass band while at medical school to cross-cultural chats with colleagues at meetings around the world. Always keen to engage in political and historical discussions, he's acutely aware of the pressures building on modern healthcare and particularly oncology.

While an alternative career in Dutch politics could have been an option, his drive to be involved at the top of his chosen profession has propelled him to the position of President of the European Organisation for Research and Treatment of Cancer (EORTC) – and all the politics that entails.

At 52, he has reached a position of great influence in the oncology world, with plenty more to come. What's more, his surgical background – and an early and ongoing involvement in biomedical research – mark him out as a rare multidisciplinary operator in cancer.

Eggermont enjoyed a top school baccalaureate education in the Netherlands that took in classical and modern languages, but it was a desire to keep as many options open as possible that led him down the science path and eventually to medicine. "Originally I was on track to do biochemistry and physics – I won a Fulbright scholarship to go to the US where I did biochemistry and musicology. On my return I decided to go to medical school in Amsterdam – realising that you can still opt for a wide choice from patient care to basic biologic research."

From there, another scholarship took him to the Sorbonne, this time to study internal medicine,

ELIGIO PAONI/CONTRASTO

"I don't know many surgeons who are into drug development"

Eggermont notes ruefully that younger colleagues want more work-life balance these days

French literature and musicology (again). And ten years later, he found himself with a Fogarty fellowship at the National Cancer Institute (NCI) in the US – which of all his defining periods is probably the most important, giving him the clout to start a research career.

First, though, came the decision to select surgery instead of internal medicine. "Once I'd done my surgery rotations, it fitted so many aspects of my idea of medical practice – there is a lot of activity and decision making, and you have to live by your decisions," says Eggermont. The move into surgery also ended a free-floating time as a medical student: "Now I had to work like a dog and be totally dedicated. Once you move into the hospital you can't count the hours, and you find out if you really want to be in medicine."

Having said that, today's young doctors and surgeons do not have to work all hours as their predecessors once did – the European Union Working Time Directive does not permit it. What's more, Eggermont notes ruefully that younger colleagues want more work-life balance these days. This might not matter so much if there was a surplus of medical staff, but he believes that cut-backs in training surgeons in many specialities "have been far too deep".

"When I came into training as a resident I was the youngest of 24 here in Rotterdam – when I left I was the oldest of eight. That created a tremendous burden on us – I don't think I ever had a week below 80 hours and many above 100 or 110. That didn't really bother me personally, but now we have hit a shortage of surgeons across medicine."

The move into surgical oncology came because Eggermont found it to be one of the major branches of surgery, and he became fascinated by the challenges of tumour biology. "I knew I always wanted an academic career as well," he says, "and would do research for the rest of my life – it had to be part of the equation."

He joined Erasmus University's experimental surgery arm in 1980, and it was in 1985, through connections with America's NCI, that he landed the Fogarty fellowship to work with Steve Rosenberg, one of the pioneers of tumour immunology research. "After working in the experimental surgery lab here, I had already written a couple of papers and was working on my PhD thesis on interferon," says Eggermont. "But I knew I had to go to the US and do research there to establish myself for an academic career."

He spent 15 months at the NCI, working day and night to take advantage of a "golden opportunity". The key, he says, is that the size of the institute allowed a "total focus" on tumour biology experimentation, with each lab turning out highly instructive reports and seminars. Eggermont worked on model systems around interferon and interleukin, and says he had to do all the experiments himself. "I did not have a lab technician, which I'm grateful for – I now know what people in my own lab are doing" (although he says he couldn't have built his lab without the help of his post-doc assistant Timo ten Hagen).

Rosenberg is undoubtedly one of Eggermont's mentors. "He is a totally dedicated researcher, and I don't think I've ever seen someone manage time so effectively and remain a nice person. I have little pictures in my head about the way he works. He runs a lab with about 100 people who work extremely hard, but even if he has only five minutes to spare for you, in the last 30 seconds he will guide you to the door and there will be a conclusion. He runs an incredibly tight ship without any sign of being a dictator. He also sticks to his research and results and is not worried about doing things ten times to be sure it's what he thinks it is."

Being at a top cancer research centre was indispensable to Eggermont, and he says it would be hard for anyone to start a serious academic

career without such experience. The fact that the NCI has pictures of many Nobel prize winners in the lobby says it all, he reckons.

It was at the NCI that he realised he had to start planning to cut down his options in terms of surgery, as his research interests would not allow him to stay on top of all surgical procedures. "I knew I would have to focus further to live in two worlds: basic lab research, and the clinical arena, which is also mainly research dominated."

Returning to Rotterdam, he completed his thesis (full title – Interferon and interferon inducers in the treatment of cancer), and took a staff surgeon's post at the Daniel den Hoed Cancer Centre, one of two major cancer institutes in the Netherlands (the other is in Amsterdam). Crucially, he was also given a brief to start research in the department of surgical oncology – and was given freedom and space at the Erasmus University Medical Centre to build a lab (subsequently, the cancer centre has merged with the university hospital, and has ambitious plans for further oncology expansion).

"So I had the go ahead to set up research – but I didn't have a single test tube to even start," he says. "I was successful in obtaining grants from the Dutch Cancer Society, armed with my track record of publications, and also started working with EORTC on melanoma." (Today he is a co-ordinator of several major EORTC phase III adjuvant and metastatic melanoma trials.)

Eggermont had already decided to focus on soft tissue cancers – melanoma, sarcoma, breast and others – for both research and surgery. Melanoma straightaway became his major research interest "…because it is the prime tumour for tumour immunology. I did my thesis on tumour immunology, it's what I'd done at the NCI and where my fundamental knowledge was."

By 1992, he had the space and infrastructure needed to build his lab, and it was then that, as he puts it, "the TNF story kicks in." TNF – tumour necrosis factor – was then a "damned drug", says Eggermont, because of its toxicity. "It came with high hopes but completely failed the clinical pathway."

The triumvirate. Eggermont, elected President of the EORTC in 2003, is flanked by Françoise Meunier the Director General and Patrick Therasse, Director of the EORTC Data Centre

However, he had met Ferdy Lejeune, then working in Brussels, now at Lausanne University Hospital, through the EORTC melanoma group. "He had been doing isolated limb perfusions using TNF on top of the chemotherapy we usually use – and there were dramatic responses." The point: isolating treatment to a limb can avoid the need for an amputation with patients with sarcoma.

"There was tremendous scepticism – TNF wasn't being produced anymore. But when I saw the angiogram of a sarcoma patient administered with this local perfusion system, I was totally sold, and became one of the few believers."

Eggermont was able to offer a big sarcoma practice, whereas Lejeune was seeing more melanoma patients and relatively few sarcoma cases. "I said, 'Ferdy let's develop this together – there is tremendous opportunity for the sarcoma agenda in Rotterdam' – and I started isolated

"I was totally sold, and became one of the few believers"

limb perfusions here. We rushed through a lot of patients and it was a phenomenal success."

Since then, Eggermont and Lejeune have become big friends and have expanded the treatment to a network of about 40 cancer centres around Europe, training surgeons to carry out the technique.

After establishing this clinical practice, grant money for basic research started to roll in for animal models. In fact Eggermont has been able to invest "a couple of millions" in what is now primarily a tumour vasculature lab, studying the vessels that feed tumours. "This is fine because, with Timo ten Hagen, I have a truly unique lab in terms of models and infrastructure – I'm not just one of many tumour immunology labs competing for resources."

As he explains, the vessels that feed tumour cells are different from normal vasculature. "By manipulating this part of the tumour we can end up with much higher chemotherapeutic drug concentrations," he says.

"It's marvellously predictive of the way things work in the clinic – it's like there is a mirror between my lab and the clinic, and the TNF programme allowed us to go back and forth for new things we first discovered in the clinic but then could only ask, 'Why the hell does it work?', in the lab. And of course because we had created a number of new model systems, everyone wanted to work with us."

Lejeune, naturally, is one of Eggermont's mentors, and as he says: "Everyone needs a lucky break – and the TNF story was mine."

Another success story has been establishing both the lab and his own position in Rotterdam. He says he's managed to avoid many of the political difficulties often associated with moving up the tree. With the freedom given to him by the Daniel den Hoed Cancer Centre to be his own boss, and because he brought research money into the medical school, he says it's been a win-win for everyone. "I could not have done it this way if I'd stayed at the university hospital to patiently climb a ladder."

He's also been in pole position to participate in the merger of the cancer centre and the university hospital. "We wanted to have a larger and better supported cancer centre with all the collateral services you need for top oncology," he explains. "A cancer centre that has a subcritical mass is a danger – you may not have everything available to you such as emergency endoscopy, cardiology, top notch intensive care and so on."

Presently, the cancer centre is located separately from the main university hospital complex, but there are plans for a centre that will be one of six specialties located in new buildings (the others will include cardiovascular, trauma and other specialties).

Over the years Eggermont has reined in his surgical involvement, such that he is now only doing relatively few procedures – perhaps operating only once a week, on limb perfusions and sarcoma resections in the limb salvage programme and the development of an isolated liver perfusion programme. As he says, melanoma surgery is relatively straightforward, and in any case he places great store by giving responsibility as early as possible to younger colleagues. "They are the ones who really run hospitals," he says, adding that medical training tends to take too long and can stymie ambition.

He says that it is not in the "genes" of many surgeons – or indeed anyone in medicine – to cut back on day to day hands on involvement. But he feels that too many do delay decisions to move into what could be more interesting and important work. "Unless you are a total specialist in a disease you will not make it on the research side," he says.

He admits he has an unusual background – "I don't know many surgeons who are into drug development." However, the number of technical advances in surgery will be relatively limited, whereas the advances in cancer biology will be simply "mind boggling", especially with the availability of new models and tools to perform research. "If you have no fundamental interest in biology, you have absolutely no business in (academic) medicine."

That said, one of his primary responsibilities is to ensure that all surgery carried out by his team remains first class. "Anything else cannot be compensated for."

And he feels that the big, immediate gains for cancer healthcare would come from making top surgical oncology procedures available every-

ELIGIO PAONI/CONTRASTO

"Everyone needs a lucky break – and the TNF story was mine"

where. "There are tremendous differences in local recurrence rates depending on where you go and who operated on you – there isn't a medical oncologist or radiologist in the world who can make up on a daily basis for the damage done in hundreds of hospitals in Europe. We know from studies carried out initially in the UK, and later all over Europe, the overriding importance of training and specialising."

But once top surgery is in place, it is "more fun" for a surgeon to think biologically and be more research minded, says Eggermont. He also feels that surgeons who have no direct biological interest cannot collaborate well with medical oncologists, and become simply "plumbers and tissue providers", while the ability to work as a truly multidisciplinary team, where surgical, radiation and medical oncology are lined up "biologically" in trials and research and daily practice, can be "phenomenally effective".

Having chaired the EORTC melanoma group for six years, among other roles at the organisation, he was elected President in 2003. "When it was founded, medical oncology hardly existed, and it was visionary to have an international multidisciplinary oncology organisation to do clinical research trials," he says. "But as people are getting older and cancer and cardiovascular disease make up more than two thirds of mortality, the EORTC has become a big organisation, and it's become a lot harder to control things. And since the mid-1990s we've seen an

With Ferdy Lejeune. Together they developed a system of TNF isolated limb perfusions that is now used in around 40 cancer centres across Europe

exponential rise in the costs of doing research."

Naturally, Eggermont also mentions the impact of the European Clinical Trials Directive on oncology research, noting that the EORTC has probably taken the strongest line it can to influence how it is interpreted nationally. By hammering away at the threat of over-burdensome regulations and lack of finance for testing existing drugs in new combinations, EORTC officials have, at least, "got under the skin of Belgian politicians and made their law the most liberal in Europe." As followers of the EORTC will know, the Belgian implementation is being recommended for the rest of Europe, but Eggermont considers it at best an exercise in damage limitation.

"The EORTC is a wonderful organisation with many top talents involved – but it is all voluntary, which is both a strength and weakness. The strength is the enthusiasm – and it has helped many academic careers around Europe, mine included. But the weaker side of a voluntary organisation is making things happen. It takes a tough stomach to get protocols through all the committees these days, and on top of that we are on shifting grounds culturally – the younger generation is not willing to give up their time as we once were. Maybe they are right and we are failing to reach out to them effectively, but the end result is that it's a hell of a job to keep 100 clinical trials up and running."

While Eggermont is doing his best to promote his own young team in Rotterdam, he feels efforts should be stepped up to encourage more young oncologists to participate in EORTC activities. "We are asking department chiefs to identify people and we are always teaching in the Clinical Cancer Research Methodology Courses in Flims." The Flims Alumni Club, set up in 2001 and supported by the Federation of European Cancer Societies (FECS), the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO), is fostering the involvement of young cancer specialists in clinical and translational research through workshops and meetings.

Naturally Eggermont has positions in almost all other major cancer organisations, including the AACR and ASCO – "I have wonderful contacts in both" – and picks out, in particular, involvement with the combined NCI, EORTC and AACR scientific and programme committees, which run "the drug development meeting of the year".

Away from his work, Eggermont is a family man. Like many doctors, he met his partner, Carola, in a hospital romance – she is an endocrinologist – and they have three children, including twin girls. He candidly admits that it is his wife who runs the home and that he has to consciously set aside time to be with them as much as possible. "The main aim is to get out of Rotterdam on vacation – as long I'm here it's no good," he says. His musically ability has had to take a poor second best – "I can't even entertain myself on the piano now," he says. But he does read voraciously on his political and historical interests – American politics (he's recently been reading Henry Kissinger's *Diplomacy*), biographies and World War Two are his 'specialities'.

Politically, Eggermont describes himself as

"It's a hell of a job to keep 100 clinical trials up and running"

"The pressure is building in Europe… for us to offer people treatment even if it is of no proven benefit"

'liberal conservative' – he defines the family unit, rather than the individual, as the cornerstone of society, and certainly in healthcare terms he says a balanced view is called for.

"The pressure is building in Europe – as it has in America – for us to offer people treatment even if it is of no proven benefit, such as let's say 'fourth line chemotherapy for lung cancer'. We need evidence-based medicine to control health-care expenses and fight against a culture of 'make believe', which of course is popular with patients and which will bring income in some systems. But it is difficult – we know that if we use some oncology drugs as liberally as elsewhere we could use the whole of our budget just on one drug."

Talking of evidence, Eggermont was widely quoted in 2001 when he looked at claims made for mistletoe extract, which is still taken widely by cancer patients in Central Europe as a possible alternative therapy. In an adjuvant therapy trial in high-risk melanoma patients, those who took mistletoe did not benefit at all from this treatment, while in lymph-node-positive patients, even an increase in brain metastases was observed. But he agreed then that much larger trials would be needed to really tell whether mistletoe is harmful, benign or helps.

One place you won't find Eggermont is on the beach administering warnings to sunbathers about the dangers of skin cancer. "Don't be overzealous or missionary with your prevention messages. I think we instil too much fear and guilt into people here. We get so little sunshine and everyone feels better when the weather is nice. In Scandinavia I'm sure they're thinking of adding Prozac to drinking water." By a strange coincidence, just after Eggermont said this there was a news item in the British media about Prozac traces being found – in tap water.

"Melanoma is a relatively rare tumour," adds Eggermont. "We know the risk factors, and we are not always helping people by deluging them with information about metastatic disease – only 2–3% of people with a suspect mole may have a problem. If you can create a feeling in younger women in Europe that smoking just isn't sexy, that would be a much bigger achievement."

Eggermont's clinic may be in good hands, but his staff would like to see a bit more of him. While he's nearly always available by e-mail or phone on his travels, his diary is a nightmare to organise. Sometimes, a staffer jokes, she's tried to contact him abroad only to find he was in the office all along. "Cloning him would be a good way to solve the problem," she says.

There's no doubt he's a bit of a polymath – Eggermont mentions his 15-year-old son using all five computers in the house simultaneously to download 24/24 hours "everything that's downloadable", something he'd have done. Apart from being a good linguist, musician, historian, organiser and doctor, he knows about food and wine (although beware a Dutch man who says he can cook – they usually can't, he says).

Is there anything he can't do? Well, apparently he's a terrible golf player. But naturally, he still enjoys himself.

The twins

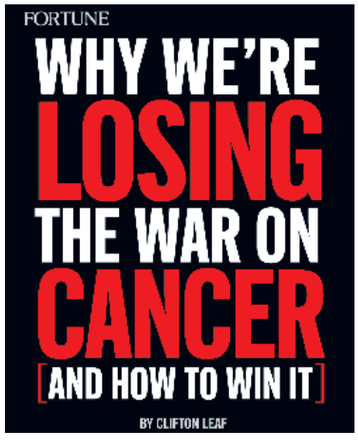
It's not a war... and we are not losing

Dispatches from the European front

Anna Wagstaff and Peter McIntyre

Thirty-three years after Nixon committed the US to defeating cancer, *Fortune* magazine talked to America's cancer gurus to find out what went wrong. The article makes depressing reading. But are things really that bleak? *Cancer World* invited leading members of Europe's cancer community to respond.

The estimated $200 billion spent on US cancer research since Nixon's National Cancer Act in 1971 has been largely wasted, and today, even controlling for age, "the percentage of Americans dying from cancer is about the same as in 1970 …and in 1950." This was the starting point of a damning indictment of progress in cancer treatment that appeared as a March cover story in *Fortune*, a leading US business magazine, under the title: "Why we're losing the war against cancer". Penned by the magazine's executive editor Clifton Leaf, the article analyses where it all went wrong and comes up with some controversial solutions.



What Went Wrong

• **Faulty models.** Researchers, he argues, work on mouse models that tell us little about the behaviour of tumours in human beings. Tumour shrinkage is accepted as the major indicator of a drug's effectiveness, but shrinkage has almost no effect on survival. Ninety percent of cancer deaths are from metastases, yet fewer than one in two hundred National Cancer Institute (NCI) grants go to research focused on metastases.

• **Regulatory straightjackets.** Slow and expensive clinical trials discourage drugs companies from taking risks and exploring radical approaches. With a time lag of 12 to 14 years and an average cost of $802 million to bring a drug to market, companies prefer to fiddle with existing compounds that buy a few extra months of survival. The system forces companies to test promising new compounds on the sickest patients, not on early stage cancer where a cure may be possible. It also hinders the development of cocktails of drugs aimed at multiple targets.

• **Dysfunctional cancer culture.** Leaf argues for a focused, collaborative effort aimed at finding a cure, arguing that it only took six years to develop the atom bomb, and eleven to land a man on the moon. Instead we

BETTMANN / CORBIS / CONTRASTO

President Nixon signs the National Cancer Act, 23 December 1971, giving him personal command of a $1.6 billion effort to find the causes and cures of cancer, which had killed 325,000 Americans that year.

have fragmented research, characterised by destructive competition and rewarding publication that contributes little to curing cancer. The legal, regulatory, academic and institutional systems combine to obstruct the development of multi-target compounds that are the most promising way forward.

How to win

Leaf sets out his prescription to win the war on cancer.

- Remove legal and regulatory constraints and give drug companies incentives to test cocktails of experimental drugs in shorter trials.
- Shift resources from advanced cancer towards detecting those at risk and treating pre-cancerous lesions before they turn into cancer
- Test drugs on people with less advanced disease.
- Transform the drug approval system.
- Move towards a funding culture that favours cooperation and focus on the big picture.

These arguments are not new inside the oncology community. Epidemiologist John C Bailar argued in the *New England Journal of Medicine* in 1986 that "some 35 years of intense effort focused largely on improving treatment must be judged a qualified failure," and in 1997, "we see little reason to change that conclusion, although this assessment must be tempered by the recognition of some areas of important progress."

He said: "Prudence requires a sceptical view of the tacit assumption that marvellous new treatments for cancer are just waiting to be discovered," and concluded that there was a pressing need to re-evaluate research strategies and to put more money into learning how to do prevention effectively.

In 2002 in the *British Medical Journal*, Italian pharmacologists Silvio Garattini and Vittorio Bertele alleged that new anticancer drugs reaching the European market between 1995 and 2000 offered no substantial advantages over existing drugs but cost many times more. They concluded: "there is little to justify some of the promises made to the public."

The *Fortune* article took such arguments to a broader arena, raised the level of polemic and included the new generation of targeted drugs in its sights. And in place of the "cancer breakthrough" stories it has run in the past, it flagged up more and quicker trials of cocktails of experimental drugs at an earlier stage, and mass screening, as the new way forward.

But are we losing the war on cancer? And are more clinical trials combined with a programme of mass screening really the panacea? *Cancer World* posed this question to leading figures from the European cancer community, and asked what they feel are the major obstacles to progress and the key changes they would like to see.

The view from Europe

Our sample of 14 experts was drawn from the worlds of clinical treatment, research, regulation, pharmaceutical industry, nursing, and patient advocacy. They represent, without doubt, the voices of experience.

Every one could give a masterclass on the daily struggle with cancer, each coming from a different perspective. But from behind this diversity of viewpoints and insights there emerges a consensus about the nature of the problem that allows conclusions to be drawn about where Europe should be focusing its efforts.

The first area of agreement is that cancer is massively more complex than any known disease including HIV. Trialling as many combinations of unproven compounds as possible in the hope that you 'strike lucky' is therefore unlikely to prove successful.

The second is a sense of confidence that increasing knowledge about the genetic origins and mechanisms of cancers will eventually translate into effective methods of control: we know where we are going, and have some idea of how to get there. However, the idea that we already know enough to identify the early stages of cancer through mass screening programmes, or know how to respond to danger signs, is wide of the mark.

Professor Mariano Barbacid of the Centro Nacional de Investigaciones Oncológicas (CNIO) in Spain

EPIDEMIOLOGIST

Peter Boyle

Director of the International Agency for Cancer Research, France

■ The significant progress in reducing mortality from cancer has virtually all come from public health interventions.

■ I know how to save 400–500,000 deaths per year in Europe. You just stop people smoking today.

■ As a society, I think we fund too much very basic biological research under the disguise of cancer research.

ONCOLOGIST

Jonas Bergh

Professor of Clinical and Molecular Oncology, Radiumhemmet, Stockholm, Sweden

- The search for accurate therapy-predictive biomarkers and surrogate markers should be given highest priority. We need screening methods that are rapid and cheap so you can screen large populations to find the very few who will benefit from therapy.
- We need more biopsies of metastases. They may be dissimilar to the primary tumour, which may affect treatment selection.
- Extensive collaboration is needed within the industry and acadaemia, because cancer is heterogeneous with multiple genetic alteration and needs to be hit with multiple drugs hitting multiple targets with an individually tailored therapy strategy.

summed up the feelings of many about the solutions proposed in the *Fortune* article: "…some of them are impossible; some are unethical and some are just difficult and don't work. If we were to implement them we would be worse off than we are in today's world."

However, many of our experts expressed sympathy with the general concerns in the *Fortune* article. There is a worry that many of the new drugs hitting the markets bring scant benefits at a cost to public health systems that could prove unsustainable. Many experts believe there is much to be done to improve the effectiveness of research. Serious questions were also raised about whether some of the money spent on new drugs might not be better spent improving the quality of Europe's cancer services, from prevention, screening and early diagnosis to treatment and palliative care.

There is clearly a debate to be had – one that requires the voices of patients and the public as well as experts. The views presented in this article are an important contribution to this debate. We hope it will encourage more people to join in.

Winning or losing?

Our team of experts agreed that in order to evaluate our progress, or lack of it, in controlling cancer, we need to understand what we are dealing with. First of all, cancer is primarily a disease of the elderly, and because people are living longer than they used to, cancer rates are going up. In effect, cancer statistics suffer from improvements in the general health of the population resulting from better prevention and treatment of fatal conditions such as heart disease and stroke. To characterise this as a failure, argues Barbacid, is like arguing that "medicine in the 20th century did not improve because the same number of people are dying – which is 100% of them."

The second point of agreement is that the 150–200 diseases collectively known as cancer are astronomically complex. Tumours look the same but have a different molecular structures in different people. Five, ten or more oncogenes may mutate in different ways according to rules we do not yet understand. Tumours are masters of adaptation with an ability to stay ahead of the chasing pack.

As Professor Mario Dicato from the Centre Hospitalier in Luxembourg puts it: "The whole biology and genetics of cancer is like a crime story. The cancer cell is a fantastic Darwinian model. The cancer cell does not have to respect anything in the hierarchy of cell organisation. Normal life is about aging but cancer just promotes its own immortality."

And so breast cancers, for example, metastasise into the bones and other organs, effectively becoming completely different tumours. Looked at from that perspective it becomes easier to see why the longed-for "cancer breakthrough" has evaded us for so long.

And yet the story told by the statistics is one of steady progress in controlling

PATIENT ADVOCATE

Lynn Faulds Wood

Founder of Lynn's Bowel Cancer Campaign, UK

- There's no question that we would save most lives if we focused on prevention, but there's no money in it. All the money is at the wrong end of the disease.
- I would introduce flexible sigmoidoscopy for colorectal cancer, and I would also sing out loud to the nation the benefits of walking.
- Give us genuine information about costs, benefits, side-effects and quality of life.

CANCER NURSE

Nora Kearney

Professor of Cancer Care, University of Stirling, Scotland

■ We have to start involving those whose voices wouldn't normally be heard. …We need to say: this is the resource we have – if you want to do mass screening for cancer, we can't treat heart disease. …We need to start this dialogue.

■ We need to sit down – as scientists, clinicians, regulators and industry – and sort out our priorities, pool our resources and start work on those collaboratively.

■ [The war analogy] led to a very close focus on cure, rather than prevention, supportive care, the process of the illness and how to manage it.

cancer – slow for some tumours, faster for others.

Professor Gordon McVie, of the European Institute of Oncology, Milan, points to figures from the UK showing that five-year survival rates in breast cancer have improved by 24% in the last 12 years, and in England and Wales mortality figures for all cancers together have shown improvements for each successive five-year period for 25 years. "That doesn't sound to me like losing anything."

It all adds up to around a 12% decrease in deaths from cancer over the past 20–30 years, according to Dr George Blackledge, Clinical Vice-President of AstraZeneca. In the face of the increase in people being diagnosed with cancer, he said, "it is actually rather encouraging."

What the statistics don't show is how much of this progress is due to prevention, screening and early detection, and how much is down to improved treatment.

Professor Peter Boyle, an epidemiologist who heads the International Agency for Cancer Research (IARC) in Lyon, puts the decline in cancer rates in Europe almost all down to public health measures, particularly tobacco cessation, with cervical and breast cancer screening also playing a role. He points to last year's review of the Europe Against Cancer Programme, which found a 9% drop in the number of people being diagnosed with cancer compared to 1985. He gives scant credit to improved medical therapies. "There has been no significant breakthrough in treatment in the past 30 years, since cisplatin was introduced for testicular cancer," he says.

His views are partly borne out by the experience of Nora Kearney, a Professor of Cancer Care at Stirling University. As part of her research, she recently returned to clinical work on a part-time basis, and says she found that little had changed. "It's terribly disappointing to come back after 12 years only to find that we are still giving largely the same regimes for most of the common tumour types."

Yet while the high hopes for a series of rapid breakthroughs that followed the introduction of drugs like cisplatin and the MOPP regimen for non-Hodgkin's lymphoma have faded, many experts warn against dismissing the progress that has been made through the cumulative effect of little steps.

This is the case made by Professor Jonas Bergh, a breast cancer specialist at Stockholm's Karolinska hospital. "If you use tamoxifen for 1–2 years, you have a survival gain in receptor-positive patients, if you use it for five years you have further gain. If you use CMF chemotherapy you have a survival gain, and if you add in anthracycline you have a further small gain. If you add taxanes you very likely have a further gain. Here you have small steps which together lead to a mortality reduction in the order of 30% or 40%."

Dicato says he is sceptical about the

ONCOLOGIST

Gordon McVie

European Institute of Oncology, Italy

■ I can't think of a more exciting field for a young person to go into than cancer research at the moment. It's absolutely bursting out all over.

■ I'd start with intelligent people and a career structure that is attractive to getting the brightest brains into the area of cancer research – people with completely different skills from the present generation of cancer researchers.

■ Biotechnology companies are a totally neglected area in the [*Fortune*] article. If I had any extra money, this is where I would put it.

value of "another fancy drug" on the market, but he too points to steady progress. "We have more than doubled the median survival in colorectal metastatic cancer over the past ten years, from around 8–10 months to something like 20–25 months. It would not be preposterous to say we will double it over the next ten years, to 50 months. It will continue to be small steps because since Lourdes there have not been many miracles."

One of the steps in this story has been the use of Erbitux [cetuximab] which, says Dicato, when used in combination with an older drug, has shown a response in 30–50% of patients with advanced metastatic disease.

And although Blackledge from AstraZeneca agrees that early detection is the key to successful treatment in many cancers, he insists that drugs also play their part. "There are probably 600,000 women alive in the world today who would otherwise be dead if it were not for tamoxifen.

"I think Mr Leaf has quite some cheek in writing such a pessimistic paper [the *Fortune* article] because he was treated and cured for Hodgkin's disease using exactly the techniques that he criticises so strongly. It is not one or two cases, it is tens of thousands of people who have been truly cured and certainly hundreds of thousands of people who have had their lives extended."

More important than whether the glass of past progress is half empty (far slower than we had hoped) or half full (steady progress through small steps) is the question of how our experts see the future. On this question there seems to be not just a consensus, but a real excitement that our ability to identify the genetic mutation responsible for individual tumours will, in time, enable us to develop effective targeted therapies.

Even Boyle, who is the most dismissive of past progress in drug therapies, is upbeat. "We are entering a wonderful new phase, with marvellous technologies and innovations, focusing on genetic defects. I'm very hopeful these will turn into new magic bullets for certain types of cancer."

Glivec (imantinib) is one of the most well-known of the new generation of targeted drugs. Developed and brought to market for chronic myeloid leukaemia (CML), it proved so effective that its approval had to be rushed through under massive pressure from patients and clinicians. Since then, it has been shown to be effective in a rare stomach cancer, gastrointestinal stromal tumour (GIST), for which there are few alternative treatments.

Glivec was dismissed in the *Fortune* article on the grounds that CML is an unusually non-aggressive and simple cancer, and anyway some tumours had developed an immunity to its effects.

None of our experts accepted these arguments. Barbacid, who was involved in the discovery of the first oncogene, and has particular expertise in the area of targeted treatments, argues that whether CML is aggressive or not is neither here nor there. The point is that the drug targets the gene that causes it, and that gives hope for the future. "This is the first example of therapy of a cell molecule that blocks the action of a specific oncogene."

Iressa (gefitnib) is another drug that shows that targeted therapies can be extremely effective. The drug was developed for patients with lung cancer, and early on there were doubts about its effectiveness (which were highlighted in the *Fortune* article).

This is a drug about which Barbacid had severe doubts. It was developed, he says, against the EGFR (epithelial growth factor receptor), and there was no evidence that this mutated in lung cancer. However, after the drug showed benefits, it was discovered this year that a small percentage of lung cancers do have mutated EGFRs. "Iressa is a wonderful story," says Barbacid. "So far there is a perfect correlation between response to the drug and the mutation."

Glivec and Iressa form part of a growing evidence that targeted therapies can work, and that increasing knowledge about the genetics and cellular mechanisms of tumours will in time transform survival rates. The question

REGULATOR

Isabelle Moulon

Head of Safety and Efficacy of Medicines, European Medicines Agency (EMEA), UK

■ Things are moving on. We need to look at different sorts of drugs, we need to look at different designs, different end points, surrogate markers, biomarkers, and take all these things into account.

■ If it is proven that a biomarker is a good marker of survival… we will accept it. We have already done that in the HIV field.

■ We need more coordination between the work of research, industry and the regulators… on where we want to go and how we want to get there.

Ten suggestions for improving cancer control in Europe

THE OBSTACLES THE SOLUTIONS

1

Europe has paid only lip service to prevention. Efforts remain limited and often ineffective.

Focus more attention on prevention – the single biggest factor behind the drop in cancer deaths in past decades. Invest in research to show what works best. Target prevention programmes to specific groups and sharpen the messages.

2

We have no way of screening effectively for the majority of cancers.

Prioritise search for effective screening methods and introduce more high-quality programmes where they are known to work.

3

The public and patients are poorly informed which can delay diagnosis and make it harder for patients to live with their disease.

Educate the public about risks and symptoms. Promote an understanding of cancer as many diseases, most of which are chronic and can be managed using a variety of treatment options. Offer patients information, tailored to their needs and preferences, to allow them make informed decisions about treatment options, some of which offer a difficult choice between potential extra survival and quality of life.

4

Market pressures can be poorly aligned with clinical priorities. A risk-averse pharmaceutical industry has little incentive to look for innovative treatments that make a radical difference. It focuses on the most common cancers and the biggest markets. Rarer cancers, including paediatric cancers, can be overlooked. There are commercial and legal barriers to testing drugs in combination. The demands of commercial confidentiality lead to wasteful duplication.

The industry, academic researchers, clinicians, and regulators need to get together and discuss, in a public and transparent dialogue, how to work together to develop effective drugs more quickly. Full publication of the results of both positive and negative clinical trials should be mandatory. The industry should be encouraged by a combination of incentives and regulation to test promising drugs in rarer cancers (which in the new world of tumour genetic profiling, may eventually include all tumour types).

5

Research models are inadequate.

Clinicians, academic researchers, regulators and the industry should seek to agree on a way forward. Possible priorities include finding: better models than fast-growing single-gene tumours in mice; pre-signs of cancer that open new opportunities for screening; biomarkers that predict survival better than tumour shrinkage, and targets in primary tumours and metastases that may respond to new therapies.

6

Clinical research in the academic setting, where it is easier to collaborate and focus on clinical priorities, is stifled by bureaucracy, exacerbated by the EU's Clinical Trials Directive. It is hard to get patients to join trials. State funding for cancer research is concentrated in basic science rather than clinical research. The European research effort is too fragmented and nationally focused.

Increase and coordinate public and charitable funding for clinical multimodality research. Reduce the burden of bureaucracy. Monitor the impact of the EU's Clinical Trials Directive and press for an early rethink. Let patients know what clinical trials are happening and where. Explain to patients what each could gain from participating. Work towards a single European cancer registry and a Europe-wide approach to research.

7

People are dying unnecessarily due to inadequate cancer care. Non-specialist surgeons in general hospitals too often fail patients.

Concentrate treatment in specialist settings using a multidisciplinary approach covering surgery, radiotherapy and drugs. Spend money on setting high standards for clinical care and bring all practitioners up to these levels. Ensure that complicated cancer surgery is performed by surgeons with the required expertise.

8

Existing knowledge and techniques are not disseminated effectively.

Invest in translating knowledge into practice and provide continuous updates for doctors and nurses.

9

Research will be stifled if it fails to attract the best young scientists of the future.

Encourage a new generation to enter cancer research with skills for the new era of genomics. Offer good career structures. Select people by interview and peer review rather than by their publication record.

10

We can't do everything. If we invest more public money in clinical research we may not be able to fund increasingly expensive drugs for a growing number of patients. If we reshape services based on specialist cancer centres we may not be able to fund every new screening programme.

These are priorities only the public has the right to decide. We need an open, inclusive and well-informed debate about options and their implications. *Fortune* raised these issues among its elite American readership. We must find ways to promote the debate across all levels of European society.

What do you think? Where should we concentrate limited resources? How do we present the issues to the public and stimulate debate? Send your suggestions, views and comments to the Editor at editor@esoncology.org, and we will publish them in a future issue.

ONCO-HAEMATOLOGIST

Franco Cavalli

Istituto Oncologica della Svizzera Italiana, Switzerland

■ Winning the war on cancer would mean that we know almost everything about the most hidden secrets of life.

■ There is no other field of medicine where cooperation is so well structured as in cancer.

■ I think [regulators] have set the bar a bit too low. If you set the bar a bit higher, then you will oblige the pharmaceutical companies to develop research to come up with significantly better drugs.

is, as ever, how much time? And is there anything we can do to speed up the process?

Obstacles to progress

We asked our European experts what they saw as barriers to faster progress, and in particular, whether they agreed with the cited problems of faulty models, lack of collaboration, heavy-handed regulation and a dysfunctional cancer culture.

Their responses generally reveal frustration that such a large proportion of cancer research is in the private sector, where barriers to sharing information and collaboration are greatest. Pharmaceutical companies have much less incentive to develop drugs for rare cancers – or indeed for small sub-groups of patients within the major cancers. Interestingly, the drugs companies acknowledge difficulty in reconciling their commercial imperatives with clinical research priorities. Many of the other challenges cited are common to the academic researchers, the industry, regulators and clinicians alike; such as identifying new biomarkers, finding more effective ways of testing drugs, testing combinations of targeted drugs, and increasing public understanding about the nature of cancer and cancer treatments. There was a feeling that in these areas at least there could be great scope for working more closely together.

COLLABORATING IN THE LABS

The need to improve collaboration was widely accepted – but not everyone agreed on the main obstacles.

Boyle, who as head of the IARC is trying to bring together the directors of the world's national cancer institutes to reduce duplication in clinically oriented research, believes that fragmentation of the European cancer research effort is a major problem.

"If the NCI decides to create a huge proteomic centre for the US, they'll put big investment into it, and they'll get the best people and they'll set the thing up. If Europe decided to do that, we won't have one European proteomic centre, we'll have a small one in the UK, a small one in France, and a tiny one in Greece and so on. While the US benefits from having a population of 250 million to draw the best experts from at national level, in Europe we have a population of 500 million, but we don't have the impact, because we think like a series of different countries."

He believes that the recent establishment of a European Research Council, and the possibility of a European Medical Research Council, are steps in the right direction. "This will reduce the fragmentation in how government research money is spent. But it won't apply to national charity funds, which accounts for most of the research money. We still won't have the same pot of money available to every researcher in Europe, as they have in the US."

However, McVie, who until recently was head of the UK Cancer Research

PHARMACEUTICAL EXECUTIVE

George Blackledge

Clinical Vice-President of AstraZeneca, UK

■ Last year we did more than 150 deals with other companies to work together to deliver newer treatments and look at combinations of treatments.

■ Mr Leaf has quite some cheek writing such a pessimistic paper because he was cured of Hodgkin's disease using exactly the techniques that he criticises so strongly.

■ We believe in attacking the disease at an earlier stage, but you have to do it in a safe way because you could damage a lot of people if you get it wrong.

PHARMACOLOGIST

Giovanni Apolone

Head of the Laboratory of Translational Research, Mario Negri Institute for Pharmacological Research, Italy

■ If you spend too much money on this kind of drug you do not have money to increase the numbers of good physicians able to give the best treatment to patients.

■ I agree with the general message of the [*Fortune*] article. Our capability to cure or postpone the death of people with metastasis is very poor.

■ We have to educate people that there is no magic way to cure such a complex disease and most new drugs are no better than the old ones.

Campaign, says allegations of a fragmented cancer effort are completely out of date. "Today all the major cancer research players in the US and the UK enter details of their projects on a single database, and hopefully the same will soon apply in Europe and Japan. You can go to the database and see what is happening to a particular kind of research – say metastases research in sarcoma – anywhere in these countries."

The real problem, argues McVie, lies within the industry. "The only people who still don't want to collaborate and let other people know about their research are the drug companies. The pharmaceutical industry spends $6 billion on research and development in the US alone, and we know very little about how this money is being spent," he says.

Dr Giovanni Apolone, who is head of a translational research laboratory at the Mario Negri Institute in Italy, agrees that the failure of drug companies to share their full results leads to redundancy in research. "Sometimes they have spent so much money on a given drug that at the end, even if they realise it does not have a new ability to control cancer, they keep going because it is better to have the drug on the market than not. Regulatory agencies receive the information they require to make a decision. It does not mean that the companies give regulatory bodies or the public everything the company produced over ten years. There are efforts to force pharmaceutical companies to make available to researchers and the public all the studies, but most countries give companies a right not to give information to competitors."

Blackledge from AstraZeneca says that companies do collaborate.

"Last year we did over 150 deals with other companies to access their technology and indeed to work together to deliver newer treatments and look at combinations of treatments.

"It is a question of when you start to collaborate. When you are actually finding out about a new molecule which may become a useful new drug there is a lot of work to do. We ought to make sure that it is as safe as it possibly can be and we need to do that in isolation from other things. Only then can we combine that agent with another agent. It would be irresponsible and dangerous to do anything else."

Dr Bernhard Ehmer, Leader of the Oncology Business Area at Merck, Germany, agrees that it would be good to see more collaboration between pharmaceutical companies, but points out that the legal questions of ownership and liability are very hard to resolve. He suggested that there should be more collaboration between the industry and public research institutes, acadaemia, health authorities and health insurance funds. This could be one way, he suggested, to help pharmaceutical companies overcome bureaucratic hurdles to collaboration – such as the legal issues that hinder joint research.

Ehmer shares some of the critics' concerns over revealing information. "There should be more sharing of data, including negative data," he says. "Very often you see data of experimental drugs, you only see the positive data as the negative data are not published by journals or accepted for presentation at scientific meetings."

Apolone believes that pharmaceutical companies and public institutions could work in tandem with a different responsibility for each sector. "A lot of money should be put into public and academic research to pick up promising drugs as soon as possible and study them in the public domain. The companies should demonstrate safety and activity and then comparative trials where new drugs are compared with the old ones could be done with public national institutions in conjunction with pharmaceutical companies. This would give more solid data before marketing the new drugs."

Not everyone agrees that pharmaceutical companies are the only ones who have trouble collaborating. Kearney, who has spent years conducting studies in cancer nursing, says that competition between academic institutions also works against attempts to collaborate. "To get a grant", she says, "I have

to show certain levels of 'returnable outputs', such as having my name as first author on a paper. When you work collaboratively, this doesn't always happen. Most of my research has been done collaboratively, and this fact alone almost doubles the time it takes to write a grant proposal."

She argues that there is a tremendous amount to be gained from getting scientists, clinicians, regulators, and the industry to sit down together and try to agree priorities for the next five years.

Others defended the collaborative record of cancer researchers. Professor Franco Cavalli, of the Istituto Oncologica della Svizzera Italiana, Bellinzona, Switzerland, accepts that universities find themselves under increasing pressure to patent new discoveries and compete, but argues that cooperation in cancer research is the envy of every other field of medicine. "The idea of cooperative groups arose in the field of cancer. There are national, international, continental cooperative groups and there are intergroup studies." The problem is funding. "Thirty years ago most drugs were developed in public laboratories, where cooperation is easier. Today, the state is pulling out of research and leaving it to pharmaceutical companies."

Stella Kyriakides, President of Europa Donna, the European Breast Cancer Coalition, says that the Breast International Group (BIG) is breaking down barriers. It helped to form the TransBIG group, funded by the European Commission, as a research network of 40 partners from the EU and Latin America that aims to develop tailored adjuvant treatment for breast cancer patients. Europa Donna has been accepted into partnership and given the critical task of disseminating research information through its national bodies and ensuring that women are better informed about clinical trials.

Kyriakides said: "The effort to involve institutions of many countries at a very high level of collaboration will hopefully stop this fragmentation so that they will bring individualised treatment to breast cancer patients earlier. I think it is a great success that Europa Donna, as an advocacy organisation, is a partner in this group."

McVie has concerns about other aspects of what *Fortune* called the 'dysfunctional cancer culture', in which academic qualifications and prestige publication become more important than the ability to innovate. This could limit our ability to exploit the latest knowledge and technologies. "My major concern about cancer research is not that it's not delivering – I think it is delivering. The question is whether it is going to deliver in the next 10–20 years. I think that the main stumbling block in the future will be the human resource. We are not breeding the right kind of bright young person to go into cancer research.

"I think the cancer culture, group think, the cliquiness of the grant system has something to do with it. The idea of measuring academic achievement by publication record over all else is a fact, and I think it is terrible."

MODELS AND MEASURES

If the issue of culture and collaboration within the cancer community exposed fault lines between its separate components, all our experts found common ground in their frustration with the mouse. No-one, it would seem, wants to continue to base the strategy for developing new drugs on what works in mice. However, no-one has come up with a better alternative.

Kearney hopes that a greater understanding of genetics may allow a move from the mouse towards genetic modelling, but points out that there will always be a need to test drugs for toxicity: "You can't just test untried drugs on human beings."

Barbacid argues that bypassing the mouse would increase the number of drugs that are tried out on humans. "Right now there are more than 430 drugs in clinical trials. What would happen if [mouse tests] were removed. How many would we have – 2000 drugs?" However, he agrees that the mouse model may be developing the wrong drugs. "Many drugs cure

BASIC RESEARCHER

Mariano Barbacid

Director of the Centro Nacional de Investigaciones Oncológicas (CNIO), Spain

■ Cancer is more than 150 diseases. So long as we continue to define cancer in the singular it is very difficult to communicate to lay people about the diseases.

■ One could argue that medicine in the 20th century has not improved because the same number of people died in 1900 as in 2000 – 100% of them.

■ Iressa is a wonderful story… nature has demonstrated a perfect correlation between a mutation that causes cancer and a response to a drug.

PHARMACEUTICAL EXECUTIVE

Bernhard Ehmer

Leader of the Oncology Business Area for Merck, Germany

■ If someone says we lost the war against cancer, that is premature. In the past we did not understand a lot. Only now are we in a position to attack it more precisely.

■ The development of new drugs is very slow and extremely expensive. We have to show the safety and efficacy of each component. I agree that this encourages pharmaceutical companies to be risk averse.

■ There should be a more open sharing of data, including negative data. Very often you only see the positive data and the negative data are not published.

human cancers in mice but when they go to human patients they do not do the same. They kill fast growing tumours but lung cancer can take 30 years [to develop]."

Ehmer agrees that the mouse model, which is integral to Merck's drug development work, is not ideal. "The question at the end is what conclusions do you draw? For us that is one methodology to obtain a set of data but we do not draw all our conclusions from that."

Leaf's argument that we are concentrating too much effort on late stage tumours, where the chance of a cure is very small, also met with a lot of sympathy as a basic research principle – but as Dicato points out, we need a cure for real patients, and most of them are diagnosed at a late stage. Both McVie and Boyle, however, think the charge is unjustified and out of date. They point out that an explicit focus in the US National Cancer Institute's '2015 challenge' is to try to stop the evolution of the disease at each stage "from the initial event to the preclinical event, the postclinical event and the metastatic progression."

There are also mixed views on whether we are relying too heavily on tumour shrinkage to measure a drug's effectiveness. McVie believes this charge too is out of date. The regulators who decide which drugs get approved (the Food and Drug Administration in the US and EMEA in Europe) now actively encourage drug developers to look for new biomarkers and surrogate end points that are more accurate predictors of survival," he says.

However, Apolone, who sits as an expert on EMEA's efficacy working party, says that about 50% of new drug indications submitted to the FDA last year were based on tumour shrinkage, and that the situation in Europe is similar. When the drug that shrunk the tumour is used in clinical practice "you are rarely able to see any clinically meaningful difference", he says.

Bergh believes there is far too much of a focus on shrinking tumours. "Tumour shrinkage studies cannot address the issue of the heterogeneity and constant mutation of tumours. We need to use biopsies and PET [position emission tomography] investigations to see what is really happening in the tumour. We are far too conservative at taking biopsies from metastatic lesions. Everyone takes for granted that the metastatic lesions are the same as the primary tumours, despite the fact that there are very few, if any, studies systematically studying whether this is the case."

Professor Jacek Jassem, who is Head of Oncology and Radiotherapy at the Medical University of Gdansk, strongly agrees with this approach.

RADIATION ONCOLOGIST

Jacek Jassem

Head of the Oncology and Radiotherapy Department at the Medical University of Gdansk, Poland

■ The majority of patients everywhere in the world are treated with local therapy, surgery or radiotherapy. Many receive pharmacological therapy as part of the treatment, but this is not the main approach.

■ Clinical research sometimes focuses too much on a surrogate endpoint, like response. We have to change our approach by putting more emphasis on real benefits for the patient.

■ Biological differences between tumours is an attractive and promising area of research. It is not much supported because the pharmaceutical industry want to treat all patients rather than selected patients.

PATIENT ADVOCATE

Stella Kyriakides

President of Europa Donna, the European Breast Cancer Coalition

■ We know that where we have early detection there is a better survival rate for women.

■ We are losing lives that could be saved because many European countries do not have screening programmes and state of the art treatment centres.

■ I think it is a great success that Europa Donna is a partner on the transBIG consortium bringing together 40 research centres from 21 countries.

"We do large clinical studies to detect a very tiny difference between two therapies. I think we should focus more on biological differences between the tumours that give us suggestions that one therapy might be much better in this particular tumour than another based on this biological or molecular marker. This is an area of research which to my mind is very attractive and very promising, but is not that much supported by the industry because they want all patients to be treated with new drugs rather than selected patients."

Not everyone is so dismissive of tumour shrinkage. Blackledge argues that "It is a great start. By and large once you start shrinking tumours you know you have got something that is of potential benefit." But in the end, he agrees, drugs are measured by their ability to affect the time until the cancer comes back, quality of life, and survival. Cavalli agrees that shrinkage is a significant measure. "It is true that most people die from metastases, but in most tumours, shrinkage of tumour goes in parallel with shrinkage of metastases. We can measure shrinkage of the tumour much more easily than shrinkage of metastases, which sometimes we can't even measure by PET scan."

THE REGULATORY STRAIGHTJACKET

If there was one culprit singled out by the *Fortune* article for blame over the lack of progress in new treatments over the past years, it was the clinical trials system overseen by regulatory authorities.

The system is slow, expensive and inflexible, argued the article, which deters drugs companies from taking risks, or innovating with cocktails of experimental targeted drugs in early disease.

Ehmer, from Merck, says "We must be very honest, initially we mostly go for incremental improvements because of the regulation and the costs of long and risky clinical development. We like to see increased efficacy or a better safety profile in advanced disease before we embark on studies with new combinations or in earlier disease." He points out that regulators usually ask the companies to prove the usefulness of each ingredient in a trial of a cocktail of drugs, even though it may only be the combination that proves effective.

Dr Isabelle Moulon, from EMEA, says that effective multi-target treatments for HIV were developed under the same regulatory system. She believes that recent changes in European approval procedures have introduced as much flexibility as is consistent with the public interest. Cancer drug approval in Europe is now channelled through a single agency (EMEA), and a number of fast-track procedures have been introduced. These include accelerated approval where a drug is very promising, early approval for "compassionate use", and conditional approval for use in a life-threatening disease, where a drug has been shown to be safe. EMEA has started discussing and exchanging information with the FDA in order to streamline companies' development programmes and the approval process. Moulon points out that EMEA has set up expert advisory groups for all the new technologies and says drug developers are now encouraged to discuss designs early in the process. But she insists that public safety must come first. "You have to remember where we came from. It was the catastrophe with thalidomide that led to the first European law on regulation.

"Most of the products used in cancer are still very toxic and we need to be careful what we do to patients."

In addition to such ethical problems, the slow time to robust results, and commercial and legal obstacles to collaboration between companies, tended to be cited as the real obstacles to Leaf's strategy of testing cocktails of unproven drugs on early-stage cancers.

SERENDIPITY

Most experts believe combinations of drugs aimed at multiple targets is where the future lies. But testing unproven combinations on early stage patients is not the answer. Serendipity is not a strategy. Bergh asks: "If there is an effect or any side-effects, how

are you going to tell which drug is responsible?"
Boyle is even less impressed. "I really don't think that rooting around in the bottom of the cytotoxic barrel, trying any combination we can get our hands on, is going to take us further forward. We did that in the 1980s. Since then we've been focusing on developing more effective and scientifically plausible approaches."
Cavalli agrees: "We simply do not understand enough about the molecular biology of these tumours to put together cocktails that can attack multiple targets. We need to improve our knowledge of the biology of the disease and that takes time."
Cavalli does blame regulatory authorities for some of the slow rate of progress – not because they are inflexible, but because they are too lax. "I think recently the regulators have made it too easy to get approval for drugs that are little better than what is already on the market. If you set the bar a bit higher, then you will oblige the pharmaceutical companies to develop research to come up with drugs that really make a difference."
Cavalli is not alone in wanting the drug companies to aim higher. Boyle suggests: "One way to deal with this could be to limit how many drugs of any one type can be on the market at any one time. In China, an extreme example, they only allow one drug in each class on the market."
All our experts cited the European Clinical Trials Directive as a brake on future progress. However, they point out that the directive is the work of the European Commission, and cannot be blamed on the regulatory agencies.

Europe's recipe for success

European experts agree that our ability to genetically profile individual tumours and analyse what is going on at a molecular level will eventually transform our ability to control, if not cure, cancer. But it will take time.
"Thirty years ago we did not know a single gene that mutated to cause cancer," says Barbacid. "We did not even know for sure – although we suspected it – that human cancer was caused by mutations in our genes. The first human oncogene was isolated in 1982. Now we have identified more than 260 different genes."
But the full story about how oncogenes mutate and how individual patients react still has to be unravelled. "…There must be some rules, but we still don't understand them," he says.
Bergh wants to see more early biopsies done in human cancers, including metastases, to develop our understanding of tumour progression. He would also prioritise finding ways of identifying patients who will respond to given therapies and ensuring drugs are administered in the correct dosage. Encouraging and investing in the next generation of cancer researchers – especially biometricians, bioanalysts and biostatisticians – is high on McVie's list of priorities. He also argues that we should be looking to the biotechnology sector rather than the risk-averse pharmaceutical industry for novel and imaginative approaches to drug development.
Moulon would like greater coordination between the work of research, industry and the regulators "so we can agree on where we want to go and how we want to do it." This is also highlighted by Kearney, who points to the newly established UK National Cancer Research Institute as a hopeful development.
Cavalli wants European governments to assume greater responsibility for funding research, rather than ceding the territory to the pharmaceutical industry. Drugs companies, he argues, start by thinking about the easiest way to get a drug approved for the largest market – the three or four most common cancers – and true collaboration is incompatible with their duties to their shareholders. "We have a wonderful structure of cooperative groups carrying out clinical studies in both rare and common cancers, but they have less and less money. Increasing support to these groups is one important way we could speed up our success."

MEDICAL ONCOLOGIST

Mario Dicato

Specialist and in Haematology and Oncology, Centre Hospitalier, Luxembourg

■ The surgeon is a prime factor for survival. If you have a surgeon without experience you will not recoup that by any kind of drug or other therapy.

■ It is certainly true that some drugs are more sexy and fashionable. After a number of years you realise it is essentially doing the same thing as the less fashionable, older, cheaper drug.

■ If you have a limited amount of money, my answer would be not to look for another fancy drug but to push early detection as much as possible.

Some fear that the trend towards targeted drugs may lead pharmaceutical companies to abandon cancer markets as too fragmented and focus on diseases more susceptible to "blockbuster" profit earners. Iressa, after all, was trialled for lung cancer patients in general – it only later became apparent that it works only for a minority.

SCREENING AND EARLY DETECTION

Our experts estimate the time it will take to control most cancers at between 50 and 100 years. A number question whether in the mean time we should focus so many resources on the search for a cure, while neglecting other opportunities.

Most agree that there should be more emphasis on early detection – including detection of pre-carcinogenic lesions that are strong predictors of cancer. But there was a consensus that blanket screening is undesirable and unworkable. Kearney says "We need to be more focused. We should keep looking for biomarkers of certain tumour types and test those in small populations at high risk."

McVie echoes her point. "There is no evidence that blanket screening will be any better than an intelligent hypothesis driven approach to the same issues."

Bergh fears that a sudden change of approach could just be another way to spend money without results. "The cost of breast cancer screening is already contentious. We need to find a system that works not just in rich countries like the US, but over the whole world. We need to find methods that are rapid and cheap so you can screen large populations to find the very few who will benefit. More importantly, we need to stimulate research into how you cure lesions once you've found them."

Lynn Faulds Wood, a former patient and now a campaigner, believes that an effective screening strategy for colorectal cancer has been available for almost 30 years, but has been passed over. Flexible sigmoidoscopy, a short form of colonscopy, has dramatically increased the rate of early detection in California. It is cheap, takes five minutes, can be carried out by nurses, needs to be done only once or twice in a lifetime, and can pick up 60% of colorectal cancers, and most cancers in the rectum.

Prevention, too, could be given a higher priority. Boyle argues that if Europeans stopped smoking today, this would save 400,000–500,000 lives a year in 15 years time. Jassem, who works in Poland where money for patient care is particularly short, agrees. "We are trying to save lung cancer patients using very expensive medical therapy, whereas we can achieve far more by being more effective in primary prevention."

Kearney says "We've been paying lip service to prevention for the past 20 years across Europe. We have the Code Against Cancer and targets for reducing incidence. But if you look at things like smoking and diet and lifestyle, current health promotion strategies are just not working. The prospect of getting cancer in 30 years time is not an issue for young people."

Faulds Wood agrees. "We've got to be more creative at relating to youngsters who pride themselves in being reckless and bad, and don't think about their middle age." When she attended the first meeting of the UK policy advisory group on colorectal cancer, she was told that prevention was not part of their brief. "Every policy group dealing with cancer in every country should put prevention at the core of their being, and then work from there," she says.

QUALITY OF CARE

It was also pointed out that a great many lives could be saved by improving the quality of treatment using existing methods and knowledge. Jassem says "The majority of patients everywhere in the world are treated with local therapy, surgery or radiotherapy. Many will receive drugs as part of the treatment but this is not the main approach. If you take into account the proportion cured by radiotherapy and the proportion by drugs, the number of studies of radiotherapy is relatively low. These studies are not sponsored by the industry. They are mainly academic studies and face many difficulties not only due to poor financing but problems related to bureaucratic regulations."

He calls for better integration of the different approaches to cancer. "The final outcome consists of several aspects: prevention, early detection and treatment. We oncologists mainly deal with diagnosed patients and it is not easy to do all these things under one roof. But it should be a concerted action and this is what we are missing on a global scale."

There is growing evidence to show that the quality of surgery in cancer is critical to survival. Dicato cites a recent Dutch study on colorectal cancer showing the prime importance of surgical skill, especially in rectal cancer, and adds: "The surgeon is just as much a prime actor in cancer of the breast and the lung because if you don't get to a surgeon there is no hope whatsoever. If you have lung cancer that is inoperable then you start counting in months and maybe the drugs give you a few more weeks."

Dicato would give a stronger push to prevention and early detection,

"rather than wait for advanced disease and then come in with complicated and expensive drugs." But every day in his hospital he sees why this cannot be the only strategy. "The reality is that the stream of patients is endless who need chemotherapy because they have advanced cancer and they come at a point where we are beyond screening. Even if I am convinced it would be better to prevent advanced disease and see them earlier on, I still have all these patients every day who don't fit that category."

Kyriakides says that since we do not know how to prevent breast cancer, we have to focus on early detection and treatment. "The European Union statistics say that we have a new diagnosis every 2.5 minutes and every 7 minutes a woman loses her life. Our primary goal is to fight the battle against breast cancer not just in terms of finding a cure, but also to improve the life conditions of women and the few men living with the disease.

"We are advocating for national screening programmes which adhere to the European screening guidelines, and for breast cancer to be treated in centres of excellence as breast units which are accredited and meet the European guidelines for treatment. Then women have the best chances of good long term survival, and in many cases cure, when it is detected very early."

Apolone would make his priority better trained doctors and better facilities. "Of course it is important to have good research. It is also important to have money to take care of the disease in all the patients in all the cities and villages of Italy. It is assumed that the translation of knowledge into practice is automatic, but that is not true. You have to allocate the money for education and also facilities in order to be able to give the best care to everyone. We have to split up the money between research and practice. There is a sort of competition to do that. You could improve the management of cancer patients in a short time; three, four or five years."

For people with advanced cancer there is a difficult choice to be made. Are the few extra months of life offered by many cancer drugs worth the possible damage to their quality of life? And, (even more difficult) would the money be more effectively spent on better palliative care for themselves and other cancer patients?

"If there is a recognition that people are living with cancer, then we will have to pay more attention not just to finding treatments for cure, but how to allow people the best quality of life with supportive care. We need that dialogue," says Kearney.

Faulds Wood, who is Chairman of the European Cancer Patient Coalition, agrees. "My son was three years old when I was diagnosed. The fear that you are going to die, leaving that child without a mother or a father, is incredibly strong, and you would deal with the devil to survive. But we need to be more honest with patients about how much extra time they may get, what it costs the country and what it costs them in terms of the way they feel. I don't think that honesty is there at the moment.

"Give us genuine information about the likely benefits, and the costs to the health service and to your quality of life.

"I would like to see patients getting together to listen to expert opinions and thrash this issue out."

Apolone too believes that choices have to be made. "If you spend too much money on this kind of drug you do not have the money to increase the number of good physicians able to give the best treatment to patients. The problem is not just physicians but also public opinion and the families. If we send out the message that the only solution is to have a major new drug, people ask for the drugs. We have to educate people that there is no magic way to cure such a complex disease, and most of the time new drugs are no better than the old ones."

Maybe this sounds like surrender, or maybe it is shifting the battle ground, or maybe it was never a war in the first place.

"This whole idea of losing or winning a war is a very American one," says Cavalli. "This was the big mistake that was made when President Nixon declared that in 20 years we will have conquered cancers like we were able to conquer the moon. Winning the war would mean that we know almost everything about the most hidden secrets of how life functions – nature would hold almost no more secrets from us. In reality, results are improving very slowly and at different speeds in different cancers. It will take 60 to 100 years till we can cure all cancers – it takes physiological time. Anyone who thinks we can win in it in five years doesn't understand the problem."

Kearney agrees: "We have to stop talking about this as a war that you win or lose, and we have got to get away from this concept that we can cure everybody with cancer, because it's not that kind of disease. Most of the resource has gone into winning the battle to find a cure, rather than prevention, supportive care, the process of the illness and how to manage it. We need to focus less on the cancer and think more about the people who have it."

Interfacing with Mogalakwena

Hewlett Packard does its bit to bridge the digital divide

Christine Haran

Many approaches are being tried to help close the gap that separates the 94% of the world who don't have access to the Internet from the 6% who do. In the case of one world leader in information technology, it is simply a question of applying their business philosophy – finding solutions to customer needs.

In the highly competitive world of global information technology, Hewlett Packard is very big. Its core business is to satisfy the demands of the world's most advanced economies for ever faster and more flexible electronic information solutions. So it can come as a surprise to find HP staff also at work in remote rural villages in India, South Africa and South America. After all, what can the maker of ten million laser jet printers offer that these villagers either need or could afford? The answer, according to Debra Dunn (in the picture), HP's Vice President of Corporate Affairs and Global Citizenship, is 'e-inclusion' – you could call it the ultimate in flexible solutions. "e-inclusion", explains Dunn, "is HP's effort to apply technology to accelerate economic development and bridge the gap between those who currently have access to technology and those who don't."

The California-based company has always had a commitment to social responsibility, and figured that it made sense to focus their contributions around their core competency, "Because we are a technology company, e-inclusion is a natural thing for us to focus on. It is about applying skills and capabilities that are related to our business to trying to narrow the income gaps in the world and help underserved communities."

Corporate philanthropy is far more widespread in the US than in Europe and takes place on an altogether different scale. A league table for 2002 published in *Business Week* magazine shows the top 56 donors accounting for a total of nearly two and a half billion dollars. HP, which comes somewhere in the middle, stands out from many of the other listed companies in the way it tailored its contribution to the requirements of a sector where knowledge, structures and systems are as important as equipment, and where new technologies can offer new ways of generating income.

"Four years ago," says Dunn, "we started marrying our philanthropic investments with our business development investments and with

Brightly painted mobile community information centres like this one bring Internet access to villages around Kuppam, southern India

staffing. Our flagship e-inclusion projects involve some contribution of equipment, but more importantly, staff on the ground to work collaboratively with local nonprofit and community organisations and government. So what we're bringing is not just financial support, but the broad assets of the company."

Getting so deeply involved in communities so different from their main markets proved a challenge. It started close to home with the digital villages initiative, aimed at bringing information technology at a community level in underserved areas in the US. "The first thing we did was put out a request for proposals to communities. We let them know the kind of thing that we were looking to do, and that we were looking for communities that had strong collaboration across sectors – government, business and nonprofit – and we were inundated with proposals."

THE FIRST THREE

Three proposals were accepted as a start. One in East Palo Alto, on the doorstep of HP's own headquarters, one near San Diego with 18 Native American tribes, and one in East Baltimore, Maryland. Each project had full-time senior-level HP staff on the ground for three years and a budget of $5 million over the same period.

The communities seemed pleased with the results. "One of the things that was very beneficial about the projects was that we didn't really have a specific solution that we were driving. We started each of the projects with a visioning session in the community, so that the key stakeholders in the community were defining the priorities for that community. We were bringing HP's technical abilities to try to address those priorities."

In the Native American project, for example, one of the big priorities for the community was to retain some of their cultural heritage. In many of the tribes, their language was only being kept alive through the elders in the community, who were aging and dying. One of the big initiatives there was to use technology to capture the stories and the language of the tribes, and now they are available for not only the current generation but for future generations as well.

Having thus gained some level of confidence and experience from these early initiatives, HP's e-inclusion projects started to venture further afield. The approach also shifted from philanthropy towards business development initiatives, working in much stronger partnerships with national governments.

"We launched two i-community projects [the 'i' stands for 'inclusion'], one in India, in a community called Kuppum, in Andhra Pradesh, southern India, and one in Mogalakwena, a rural community in the Limpopo region of South Africa. In Kuppum one of the foundations of the project is the delivery of government services through community information centres that we set up. These centres are run as entrepreneurial ventures; their business is charging for the information services that they provide. Part of the suite of services provided is government information services."

The Indian government, says Dunn, is notorious for being bureaucratic, and there are many transactions that citizens need to conduct with the government, often on a monthly basis, perhaps even more frequently. Most utilities, such as electricity, are public services and, historically, people living in rural areas had to travel fairly significant distances if they wanted something done. With long queues and inconvenient opening times, said Dunn, this sort of business consumed a lot of time that could have been used much more productively. So HP worked with the Indian government to take some of the online services that they'd already created for the cities and make them available in rural areas through the community information centres.

In some ways this job was the bread and butter of HP's business. But coming as they did from the heartland of California's Silicon Valley, staff inevitably found it quite a culture shock.

"To give an example," says Dunn, "We have a very strong time-driven sense in the business community here and in South Africa. Everybody's living off their schedule and pays a lot of attention to it. Not true in the rural community in Mogalakwena. Things as basic as making sure that people show up for meetings took some effort."

HP has also had to develop ways of training and developing technical skills in communities with a very different skills base from what they are used to back home. This has involved literacy training as well as teaching basic computer skills to people who cannot read and may or may not be numerate. Again, it is a question of finding flexible solutions, "Depending on the area, there are different resources. We partner with lots of different organisations to help build some of that capacity in the community."

So with equipment installed, systems online, operators trained, it all amounts to an impressive piece of bridge building. And yet, explains Dunn, it's still not enough to close that digital gap. This is not least because that wealth of information that you can explore via your choice of search engine if you live in Palo Alto is of little use to people in other parts of the world looking for information relevant to them, in a language they understand. Development of content has therefore been a priority in these projects.

Bridging the health divide

Of course the effects of HP's e-inclusion work go well beyond the projects themselves, because once the infrastructure is in place, it can be used for any number of initiatives, whether public, non-governmental or private. In the field of cancer, for instance, as Dr Alex Jadad of the Centre for Global eHealth Innovation described in the previous issue of *Cancer World* (September 2004), a huge effort is being put into taking advantage of the Internet to deliver information on palliative care and health promotion materials on anti-smoking tailored to communities the world over. The e-inclusion initiatives being run by HP make a vital contribution to this effort.

Dunn mentions some other health initiatives already in operation. In Mogalakwena a telemedicine project allows data and photos to be e-mailed to a physician who can then e-mail back recommendations. In Kuppam, eye testing for community members is done through a computer programme on a laptop that is part of a mobile van that travels from community to community. New mobile clinics are staffed with two physicians who provide consultation and medicine free of charge. And a new partnership between HP and UNICEF offers a photo-based software programme about pre-natal and early childhood care that is accessible at community centres or through the mobile clinics.

As a piece of philanthropy, the potential value of

all of these projects is clearly immense. But like many successful initiatives, the benefits of HP's e-inclusion programme go both ways. It is the old question, says Dunn, of knowing your market. Having high-level staff working over a three-year period with underserved local communities, and in partnership with their governments and local authorities, has given HP a unique understanding of new business opportunities that would simply be impossible to gain from an office in Palo Alto.

Most information technology solutions, she points out, have been developed based on the needs of people in the developed world and then pushed out to those who can afford them. "I think it's not new within the business world that deeply understanding the needs of your customers is key to success, but not many technology companies have invested in deeply understanding the needs of people who are further down the economic pyramid. We've asked: If you're someone living on a dollar a day – and some people in some of the villages where we're working fit that description – are there solutions that really add value to you that you would pay for? Then we have come up with business models that would be workable."

There may not be a great future, for instance, in selling digital cameras and colour laser printers to families in rural India. But many people may be willing to pay for photos on a per-photo basis, and so one of the ideas HP has been piloting in Kuppam has been helping individual entrepreneurs set up their own businesses as village photographers.

So individuals benefit, HP benefits and the local communities benefit. It all sounds very neat. For those working on the ground, however, it can hardly feel that way. In fact the prospect of parachuting in as part of a task force of high-flying American IT specialists, leaving behind the world of electronic organisers, mobile phone dependencies and business breakfast schedules, and trying to interface with rural communities whose lives are dominated by the age-old rhythms of the countryside must surely be pretty daunting.

"It is very messy to do this stuff this way," agrees Dunn, "and that is uncomfortable for most corporate organisations. And risky. It's a bet. But our experience to date would say it's been very productive bet."

HP, she feels, has taken a lot of credit for taking the risks and trying to move beyond the traditional 'we give – you receive' models of corporate philanthropy towards a more collaborative and engaged approach, focused on building capacity and creating sustainable models in the community. "I think we've got reasonable evidence that we have contributed to the communities that we're working in. The feedback we consistently get is that they've never worked this way with a company."

"Equally importantly," she adds, "we've learned a lot in terms of the dynamics and needs of these kinds of communities, and we've come up with some different approaches and different solutions. So from a business perspective, they've also been valuable to us."

Given the enormity of the digital divide, these projects may seem rather small fry. But HP hopes this is just the beginning. "We're continuing with the developing world projects," says Dunn. "We are in the process of identifying specific components of those projects that can be replicated and we are taking some of the specific business solutions that we've been working on and moving them into the marketplace."

There will be many who wish them well. Not least all those involved in the effort to use the Internet to boost global efforts to prevent cancer and improve cancer care.

"We've learned a lot in terms of the dynamics and needs of these kinds of communities"

Louis Denis: Urology's foremost free thinker

Interview by Raphaël Brenner

The son of a Belgian docker, Louis Denis, now Director of the Antwerp Oncology Centre, joined the army to get through medical school. Though often at odds with the medical establishment, he rose to the top of his field, and helped shape European oncology through his commitment to prevention, research, professional education and innovation.

From a poor background you've made it to the top in a pretty elitist profession. What has been the driving force in your career and life?

LOUIS DENIS As far as I can remember, I've always wanted to help people and fight against social injustice. For me, medicine was the natural answer. I came from a poor family – my father was a docker – so I enlisted in the Royal Military School of the Medical Services in order to be able to finish my medical studies at the University of Ghent. I dreamt of becoming a general practitioner, but the army pressured me to specialise, and that was how I came to do postgraduate studies in surgery and urology in Antwerp and the US. I feel I've been very lucky, helping other people is the least I could do to repay what society has given me.

Do you feel you've remained faithful to your beliefs in your career?

LOUIS DENIS I hope so. I love people and I love to help. Through my association with some of the great names in oncology, such as Gerry Murphy and Umberto Veronesi, I have been able to help many young urological surgeons and oncologists.

Some of them, like Andrew von Eschenbach and Tadao Kakizoe, have gone on to make great names for themselves, as Directors of the National Cancer Institutes in the US and Japan. These networks also helped me secure a grant from the Belgian Government worth two million euros to establish a new headquarters for the EORTC [European Organisation for Research and Treatment of Cancer] in 1990.

I abhor power, arrogance and elitism. As a free thinker, I have come under a lot of political pressure and manoeuvring against me, but I never compromised my beliefs and, ultimately, perseverance paid off. My success has been entirely due to my professional skills. As for money, despite the difficulties I faced, I never bartered my independence or freedom of speech for money.

You might call this ethical but, for me, it was the most natural thing to do.

At his desk. Having recently been diagnosed with prostate cancer, Denis is continuing to champion the cause of the patient – from the other side of the consulting table

Do you think the slogan 'excellence without arrogance', recently coined by Andrew von Eschenbach, is a good guideline for physicians?

LOUIS DENIS Definitely! Who are we to be arrogant? I worked hard but I was also very lucky. Call it what you want – coincidence, fate, opportunity – you need to be lucky to succeed. In the course of my specialisation, for instance, I met the right people at the right time. My boss in the US, George Prout, later Professor of Surgery at Harvard University, let me perform laboratory research as well as surgery from the start. So my four-year training in urology at the Medical College of Virginia in Richmond became a turning point in my urological career, because it gave me my enthusiasm for research and clinical trials.

I dreamt I could find a cure for some urological cancers, but I also learnt that cure or control of cancer is achieved through small steps rather than in one giant leap. I was lucky enough to participate in the very first prostate cancer trial, which was led by the great W.W. Scott of Johns Hopkins University Hospital. This is how I came to know the important urologists of the last decades on first-name terms.

But my greatest luck was in having such an excellent staff in Antwerp and Brussels, led by Pierre Nowé and Frans Keuppens. They supported my international career by providing a top-quality service to patients. They also introduced innovative surgical methods and procedures and organised dozens of seminars and meetings.

As Goethe said, "I would have been nothing without my friends."

As a tireless lecturer and founding member of the European School of Oncology, what do you feel is the most important message to convey to physicians?

LOUIS DENIS It has always been my belief that a physician should treat the person, not just the disease. This is why I strongly advocate a holistic or multidisciplinary approach. The problem is that even if oncology training today emphasises the importance of interacting with patients, science has turned medicine into a technological discipline and the more technological it becomes, the harder it is to retain the human touch.

We need to learn how to use knowledge in the best possible way, never forgetting that we are dealing with human beings who are all the more vulnerable because they are sick. Compassion is the most important aspect of a physician, not intelligence. Patients do not care about research results. They deserve heartfelt words and a warm approach. This is the real challenge – how to be warm and empathetic towards others.

The more technological it becomes,

the harder it is to retain the human touch

After a distinguished career as Head of Urology at Antwerp Hospitals and Professor of Urology at the Free University of Brussels (VUB), Denis is currently Director of the Antwerp Oncology Centre, and is pictured here with his staff

As a patient, I must confess I find hospitals depressing places

Are nurses and other support staff sufficiently trained for the task of providing information and support to patients?

LOUIS DENIS In any hospital, it is the paramedical team that has the greatest contact with the patients, so they are the ones who need the best training in how to provide effective support. In our hospitals, all the paramedical staff attend regular training sessions on the management of cancer patients. Take a nurse in charge of assigning beds to new patients – this may be a small detail, but it is an important one. Beds are assigned and consultations given according to the patient's needs. If a patient due for surgery is given a bed next to a patient who has just had an operation for a similar problem, this gives the newcomer a chance to pick up information, which could help ease their anxiety. But this

RESCUE MISSION IN DEEPEST AFRICA

In November 1964, several hundred Europeans and Americans were taken hostage by rebels in Stanleyville, Zaire. Belgian paratroopers, sent to rescue the hostages (Operation Red Dragon), parachuted onto Stanleyville Airport, with Captain Louis Denis, then Chief of the Department of Urology at Antwerp Military Hospital, serving as field surgeon. Since retiring from the army, Denis has given lectures on urology to military physicians and, next April, he is set to help launch the first European School of Oncology course on oncology for military physicians.

model works best with a good, multi-professional team supported, if possible, by members of patients organisations.

Issues around the role patients play in decisions about their own treatment are coming increasingly under the spotlight. What approach do you take at the Antwerp Oncology Centre?

LOUIS DENIS Our first aim is to make clear to patients that we see them as independent individuals and they should not be afraid to talk to their doctors as equals. It is a sad fact that there are still surgeons who deny their patients basic rights, and just tell them: "You know nothing. I am the one who's going to do the operation." Our second aim is to help patients to understand their medical problem and also to evaluate their physician. Do they feel he or she is competent? – a second opinion could be helpful here. Do they feel he or she communicates well on a human level, and allows the patient to talk and ask questions? Last but not least, given the fact that patients are not well informed, we provide them with a 'passport'. This is a booklet that gives patients a wealth of information on their disease, on the examinations they will undergo and on the management of the disease.

Support groups like Europa Uomo [the European Prostate Cancer Coalition] have changed the way patients experience their illness. The knowledge they acquire on their cancer and the reassurance they receive from doctors and other patients help to foster a more positive attitude to their illness. This sort of support also helps reduce anxiety levels, which are often a greater cause of suffering than the disease itself.

The value of PSA (prostate specific antigen) screening is another issue much under the spotlight. As international coordinator of the European randomised screening study for prostate cancer, what is your view?

LOUIS DENIS Until we have the results, which will be in three to four years, the lack of evidence on the true benefit of population screening calls for a very balanced attitude. Consider the natural history of prostate cancer: it takes 20 years for a microfocal cancer to become a clinical tumour, and it takes another 15 years for a clinical tumour to kill a patient – 35 years is a long time! Moreover, we know that 50% of men aged between 40 and 50 have a nascent (microfocal) prostate cancer and that 3% eventually die from the disease after many years. So I see no justification for offering a PSA test to an asymptomatic man, unless they are at risk – all the more so because PSA testing is unreliable and is often a pretext for a biopsy. We must remember that we are talking about healthy people! Screening has to be done responsibly: being told you have cancer can destroy your life, even though in the end you may die with the

Support groups like Europa Uomo have changed the way patients experience their illness

cancer rather than because of it. A PSA test is routinely carried out on symptomatic patients, although localised prostate cancer rarely causes symptoms. In my opinion, the test is indicated if abnormalities are found on a digital rectal examination or if a patient is anxious due to a family history of prostate disease or because of information gained via the media. Frankly, we are desperately looking for a more specific test to diagnose prostate cancer.

What is your approach to managing prostate cancer, given the rates of incontinence and impotence associated with surgery?

LOUIS DENIS Given the natural history of prostate cancer and in spite of being a surgeon, I call for caution. If we talk about a 65-year-old man in good health and with a good prognosis, we have three possibilities that are more or less equivalent: radical prostatectomy, radiotherapy (external beam radiation therapy or brachytherapy) or no treatment at all, which is often disregarded by physicians but is indeed an alternative. Active monitoring is not routinely applied, but it is justified in appropriate cases and, in these cases, we inform patients that there is a 50% chance they will require treatment depending on the evolution of the prognostic signs.

With all these treatments, there is a 95% survival rate after five years, which is normal for early prostate cancer. However, many patients exhibit some rise in their PSA level after treatment, which necessitates renewed treatment. On average, I would say that 25% of patients are overtreated and another 25% undertreated. This is of great concern, as there are often severe complications entailing impotence and incontinence, which can reach double-digit figures. But let's be clear: this is not an inevitable tragedy. With surgery as with any method, the rate of success can vary considerably depending on the skills and experience of the surgeon.

This is why I favour centres for prostate cancer treatment with multi-disciplinary staff. Lastly, among the new non-surgical alternative treatments, high-intensity focused ultrasound can be successful depending on the size of the prostate, but we need five more years of follow-up to be able to assess this method fully.

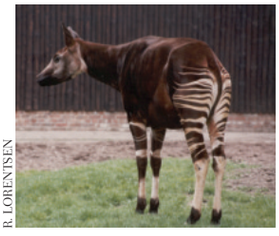
You yourself have been diagnosed with prostate cancer and you played a central role in launching Europa Uomo. Has this changed the way you see things at all?

LOUIS DENIS As a surgeon and researcher I have seen all the facets of this disease, but as a patient, I must confess I find hospitals depressing places. Neither the outside nor the inside of hospitals are welcoming or comforting to patients. I hope that, in future, architects will design smaller, more humane structures.

Regarding my own illness, I am not afraid. I have always been conscious of my mortality and I believe that living means "learning how to lose." I want champagne and Scottish bagpipers at my funeral and I want my friends to remember me as a free-thinking man. I had a marvellous life and I am blessed with a supportive family and a dozen grandchildren.

I did what I wanted to do, I said what I wanted to say and, at the age of 71, I see no reason to hang on needlessly. Seventy-five per cent of cancers appear after the age of 65, so at this age one should have the maturity to view cancer as a challenge, as an opportunity to surpass oneself, to look at things differently, and to acknowledge forces greater than oneself. Most importantly, one should fight to control the disease, with the support of sympathetic professionals.

UROLOGY FOR FOUR-LEGGED FRIENDS



R. LORENTSEN

World-famous Antwerp Zoo had a male okapi who could not copulate. Unable to identify the reasons, the veterinarians turned to Prof. Louis Denis for help. After a very delicate general anaesthesia, the examination revealed an infected foreskin. An extensive circumcision was performed and since then many little okapis have been born in various European zoos.

EIO: A truly European Centre to rival the best

Anna Wagstaff

It seemed like a gamble when the European Institute of Oncology opened in Milan ten years ago. But this centre of excellence reversed the brain drain and set some of the highest standards for patient-centred treatment and research anywhere in the world.

When the European Institute of Oncology in Milan celebrated its 10th anniversary this summer, it did so in characteristic fashion. For the month of June it played host to back-to-back meetings, gatherings and exhibitions aimed at furthering knowledge of cancer and promoting collaboration to overcome it.

A meeting of oncologists from the ten countries that had just joined the European Union; another on collaboration with Gulf Region countries. A series of meetings of patient organisations, for patients with breast cancer, prostate cancer, chronic myeloid leukaemia or gastrointestinal stromal tumour (GIST), and patients involved in an EIO trial into preventive use of tamoxifen. The European Cancer Patient Coalition held its first masterclass. There was a summit of national cancer organisations on pain in terminally ill patients. A seminar for general practitioners. A course in sentinel node mapping in breast cancer. Seminars and workshops on immunology and vaccines, on molecular targets, melanoma research, thyroid cancer, leukaemia and lymphoma. Even local children joined in, coming on school trips to see an exhibition explaining the amazing discoveries behind genomics.

After only 10 years EIO has become an international centre of excellence that can compete with any cancer institute in the world in terms of discoveries, trials, publications and the calibre of its clinical and research staff. What makes it different is the fervour with which it seeks to collaborate, educate, enthuse, and involve everyone from patients and support groups to students, graduates, general practitioners, and the general public.

Starting from scratch

The EIO is unusual among European cancer institutes in that it started with no government backing. In Italy, this was unheard of. New legislation had to be passed to lay a legal basis for a private, non-profit organisation. Independent backers had to be found to donate large sums to support a vision that would never provide a financial return, since all profits are ploughed back into research.

Top researchers, clinicians and administrators had to be attracted to work in a country that had lost many of its own best people to the US and elsewhere, where they felt able to make better

One floor above the wards, clinical and basic scientists carry out ground-breaking work in molecular oncology and genomics

use of their skills. Someone remarkable was needed to inspire the confidence to achieve this. That someone was Umberto Veronesi, the charismatic director of Italy's National Cancer Institute in Milan, who had made his name on the international stage through his development of quadrantectomy – the first major breast conserving treatment for breast cancer.

He persuaded Giuliano Amato, then Minister of the Economy, to push through the legislation, and convinced Enrico Cuccia, president of Mediobanca, one of Italy's largest merchant banks, to back the project, which opened the way to a wave of financial backers. He, too, was instrumental in convincing leading Italian émigrés and top European oncologists to sign up. Among them was Pier Paolo di Fiore, who left his job as head of laboratories at the US National Cancer Institute (NCI) to become Director of the Experimental Oncology Laboratory. With him came his colleague and renowned Italian cancer researcher, Giuseppe Pelicci, to head the Department of Experimental Oncology.

The cream of Europe

Six of the 15 original heads of departments came from outside Italy. Jean Yves Petit, the internationally renowned plastic surgeon, came from the Institut Gustave-Roussy to head the Division of Plastic and Reconstructive Surgery. The head of the Department of Surgery, Niall O'Higgins, came from University College, Dublin. Aron Goldhirsch reduced his commitments in Switzerland to head the Division of Medical Oncology, Peter Boyle came from the International Agency for Research on Cancer to head Epidemiology and Biostatistics, and Kristian Helin from Denmark to head one of the basic research labs. Finally, Luc Vanuytsel, who developed the prototype of conformal radiotherapy for prostate cancer, came from the University of Leuven in Belgium to lead the Division of Radiotherapy – the EIO became the second institute in Europe to own and operate a conformal radiotherapy machine.

Internal collaboration between all aspects of the Institute's work – patient care, basic and clinical

The Institute transformed patient attitudes towards participating in clinical trials

Open spaces and plenty of light are cornerstones of the EIO design. Architects Impregilo are now in discussions over plans for a major new cancer center in Oxford, UK

research and management reflected Veronesi's vision for European collaboration. Under the motto "Si cura meglio dove si fa ricerca" [Treatment is better where they do research], the Institute transformed patient attitudes towards participating in clinical trials.

The EIO insists that managers understand the priorities of the clinical and research side, and that clinicians and researchers understand and support the management process. This ensures that financial and administrative decisions are in line with the priorities of the Institute as a whole, and has allowed the interdivisional collaboration necessary for significant clinical studies.

The Institute is managed around the needs of cancer patients, aware that they often suffer high levels of stress, trauma and depression. Disruption to the patients' lives is minimised by keeping average admissions down to three or four days. The EIO provides the high-end diagnostics and treatment, with top clinicians and state of the art equipment, while routine follow-up is provided closer to home. With only 200 beds, EIO admitted more than 16,500 patients last year. The introduction of intraoperative radiotherapy has allowed admission times to be further cut in many cases.

Each patient is assigned a nurse and, whenever possible, nurses introduce themselves by phone before admission.

Better by design

The building minimises the gap between hospital and normal life. Gone are the traditional hospital lifts and white gloss narrow corridors that make patients feel they are being shunted helplessly around a closed building. Here, escalators travel up and down the spacious atrium, leading to wide pastel-shaded corridors which overlook a large courtyard garden. The emphasis is openness, accessibility, and normality.

Patients do not eat to a hospital timetable. Meals are available from the canteen at any time. The rooms feel more like a hotel than a hospital – no

Gone are the traditional hospital lifts and white gloss narrow corridors

Six of the first departmental heads were Italians returning from the US

more than two beds, and a TV in every room. However, this is no holiday break. Patients are encouraged to find out about their treatment and their condition, and to participate in clinical trials. TVs can show information videos, some filmed in collaboration with patients, to explain what happens during a bone scan, a CT scan or when the patient is anaesthetised.

In an effort to demystify the medical process, analytical labs have glass walls facing the escalators, so that patients can see the technicians processing blood and tissue samples.

At the time the EIO was set up, there were 92 Italian oncologists working at the NCI in Bethesda outside Washington DC.

The new Institute reversed the brain drain as it set up a department of experimental oncology, devoted purely to research. Six of the first departmental heads were Italians returning from the US. In 1995 it opened the first unit in Italy dedicated to Nuclear Medicine, and soon started hitting the scientific headlines with innovations like the avidin-biotin technique in radioimmunotherapy, which makes it possible to radioactivate only the antibodies that bind to the tumour. This work was later to yield further important progress with the discovery of receptor molecules found on the surface of some cancer cells that can be used to convey the radioactive dose exactly to the target.

In 1998, the discovery that a natural substance, retinoic acid, can block the mechanisms of action of leukaemia cells, restoring their normal function, marked the creation of the first 'molecular drug' – and earned the EIO its first publication in *Nature*. In 2001, a nanotechnology laboratory was opened which is now building 'gene chips' that will allow the expression profiles of thousands of genes to be determined simultaneously.

The Institute also rapidly built a name for clinical innovations. It perfected the ROLL technique – Radioguided Occult Lesion Localisation – a surgical technique to remove non-palpable breast lesions, and played a leading role in developing and perfecting the sentinel lymph node biopsy, which saves women from having healthy lymph glands in their breasts removed. It introduced intraoperative radiotherapy, removing the need for repeated trips to a specialist radiotherapy centre following surgery. It demonstrated that conformal radiotherapy – targeted precisely at the tumour outline – yields as good results as surgery in men with prostate cancer.

Clinical trials

The Institute led the way in chemoprevention, with a study of the use of low-dose tamoxifen in women undergoing hormone replacement therapy. Another clinical trial, published in the *Lancet* last year, revealed an important step in the early detection of lung cancer. A combination of spiral CT and positron emission tomography [PET] was able to detect even the smallest lung tumours and even allowed investigators to determine whether they are benign or malignant.

Italy, specifically Milan, has long been at the forefront of important cancer innovations – notably the quadrantectomy (radical lumpectomy), CMF and adriamycin – but cutting-edge basic science research has traditionally been the preserve of the American NCI and a handful of other major US

Professor Veronesi outside the EIO

Escalators make it easy to move around, giving the building the feel of a shopping centre or airport as much as a hospital

and European research institutes. The EIO has now claimed its place among this elite.

The Institute promotes debate on how and what scientists and physicians should communicate to the public to improve cancer prevention and to encourage a positive attitude among patients.

EIO runs seminars for journalists and its Press Office looks for ways to encourage more and better media coverage of cancer. It used the opportunity of 10th anniversary to secure feature pieces in two of Italy's top dailies.

The EIO also runs a variety of medical education programmes and specialist courses. There are regular courses for general practitioners – key to ensuring early diagnosis – and an oncology hotline offering a 24-hour free consultation service.

As Paolo Spriano, General Practitioner, said: "After ten years of training and educational activities with the EIO, I am all the more convinced that the alliance between oncologist and GP is of vital importance."

A Masters Degree in breast pathologies in collaboration with Milan University attracts students from all over Europe. The EIO also offers placements to students from the University.

Though Italian patients and the Italian health and education system directly benefit, the EIO is European in its staffing and outlook. "We knew Europe could never hope to compete with the US if our efforts were conducted country by country," said Veronesi.

The EIO has links with the Gustave-Roussy in Paris, the University of Vienna, University College Dublin, the Catalan Institute of Oncology in Barcelona, and the Swiss Italian Oncological Institute in Bellinzona. The scientific directors of each partner sit on the EIO scientific committee, ensuring a truly European outlook and facilitating cross-European collaboration. The EIO is helping to ensure that, as cancer enters the era of genomics and proteonomics, Europe will be in a strong position to play its part.

Characteristically, Veronesi, who describes the EIO as one of his children, used its 10th anniversary as an opportunity to look forward rather than back. "The research and treatment of cancer requires specialist centres in order to develop clinically and scientifically, and cancer patients need an environment that supports them through a deeply stressful and traumatic experience. My hope is that the outstanding success of the EIO in its first 10 years will help provide the vision and confidence to establish here in Italy similar centres of European excellence in the fields of neurology and cardiology."

It's a nice dream. And with Veronesi's track record, there's always a chance it might yet become reality.

El País reporter wins cancer award

The 2004 ACE Reporter Award has gone to **Mayka Sanchez**, health editor of Spain's leading daily paper, for a series of pieces she wrote on various cancer types and issues in cancer care. Below we reprint one of them, entitled: **The elderly: disenfranchised by cancer services.**

Oncologists and geriatricians alike acknowledge that for many years the elderly have been sent to the back of the queue for cancer treatment.

This phenomenon, which is widespread in developed countries, collides head on with reality that 50% of cancer patients are over 70 years of age, and 65% of Spanish citizens who die as a result of the disease are over 65. Furthermore, until very recently old age meant exclusion from clinical trials through which new therapies are tested. The recent report issued by the Civil Rights Ombudsman, which was commissioned last year by the Spanish Geriatric and Gerontological Society, confirms these statistics.

Catalonia, which has a special Life for Years programme, introduced in 1986, was the first region to launch a specific initiative aimed at improving care for the elderly. Valencia followed suit in 1995, and Castilla León in 1998. The Civil Rights Ombudsman's report lists similar initiatives that were introduced towards the end of the '90s by other communities striving to ensure fair treatment. However, according to geriatrician Juan Ignacio González Montalvo, coordinator of the report, although Spain is beginning to win a long nationwide battle to improve social and health care for the elderly, "geriatric oncology has not been a serious concern for doctors and, up until very recently, there has been much hesitation and uncertainty in treating elderly oncology patients."

González Montalvo, Head of the Geriatric Evaluation Unit at La Paz Hospital in Madrid, warns that the decision-making process regarding elderly cancer patients must strike "a careful balance between life expectancy, the efficiency and potential complications of the proposed treatment, and the effects of the illness in question." But he acknowledges that the key objective in cancer treatment for the elderly is often to maintain the patient's quality of life.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Ancianos, los marginados del tratamiento del cáncer

Un informe encargado por el Defensor del Pueblo advierte sobre diferencias en la asistencia

This story of discrimination against elderly cancer patients is a good example of how the popular press can inform people about cancer and cancer care

Myths and taboos

Figures from the National Cancer Institute (NCI) in the United States reveal that 60% of all malignant tumours occur in patients over the age of 65; approximately half of which appear in patients older than 70, and as many as a sixth in individuals over 80.

The same statistics show that the probability of a man aged between 60 and 79 developing an aggressive cancer is one in three, while it is one in five for women. The three main causes of cancer mortality in this age

RICHARD HAMILTON SMITH / CORBIS / CONTRASTO

group are lung, colon and breast tumours.

According to oncologist Manuel González Barón, Chief of the Medical Oncology Service at La Paz Hospital, age is one of the risk factors in cancer prognosis. As first author of the book *Cancer and the Elderly* (published by Masson, Barcelona 2001), González Barón writes that cancer has risen by 17% among the elderly while decreasing by 23% among adults under 65.

"Taboos, myths and moralistic viewpoints," he notes, "are rife concerning the association between cancer and ageing, and this is perhaps the reason why the problem has not been sufficiently addressed. Indeed, scientific papers that explore the various basic and clinical aspects of this association are only relatively recent."

González Barón's view is that although this association is widespread, there are no scientific findings to-date that show that cancer behaves in a different way in the elderly, or that it is more or less aggressive in younger patients. Senior citizens over 70 have nevertheless been excluded from clinical trials in general, and have been completely ignored in studies on the surgical and pharmacological treatment of cancer. The NCI statistics are therefore of little surprise: they show that mortality resulting from malignant tumours has decreased in patients under the age of 54, but is on the up in patients over 65.

As Jaime Feliu Battle, La Paz Hospital's oncologist and co-author of *Cancer and the Elderly*, explains, biological age must be considered an important factor when deciding on cancer treatment: "Mortality associated with other disease, general functional state, emotional disposition, and the stage of cancer development must take precedence over other factors when deciding upon a course of treatment."

If today the life expectancy of 70-year-old patients ranges between 12 and 16 years (according to gender), and that of 85-year-olds ranges between 5 and 7 years, why not extend survival of elderly cancer patients or even try to find a cure whenever possible? asks Hernán Cortés-Funes, Head of the Oncology Department at the Doce de Octubre Hospital in Madrid: "I have administered chemotherapy," he continues, "to patients over 90 years old, having weighed up the associated risks and benefits. There is an increasing number of studies that show that success rates of cancer treatment can be as high as those of treatment of younger patients, and that toxicity needn't necessarily be higher."

Cortés-Funes admits that age heightens the risk of cancer, simply because age naturally assumes extension of the time one is exposed to cancerous

agents. Furthermore, other endocrinological and immunological factors are also at play, since the immune system's defences decrease with age. The older the individual, the fewer T-lymphocytes they have (one of the main cell populations involved in the immunological response). It is possible that the reduction in T-lymphocytes may be associated with a disorder of the thymus and with the decrease, if not loss, of hormones secreted by this gland.

PERSONALISED THERAPY

"The elderly, just like any other age group, have a right to receive the latest available cancer treatment as opposed to a prêt-à-porter service. This can only be achieved through appropriate geriatric evaluation in order to select the correct personalised treatment," insists oncologist Manuel González Barón – a view that is echoed in the report issued by the Spanish Geriatric and Gerontological Society and the Association of Multidisciplinary Gerontology.

The recently published report commissioned by the Civil Rights Ombudsman clearly highlighted the point that "healthcare for the elderly must be of the same standard as that offered to younger patients, and the same technology, diagnostics, and therapeutics should be applied." It also states that "it is essential for the elderly to be diagnosed and treated at the earliest possible stage."

Spain's 400 geriatricians agree with the findings of the report and support the demand that there should be, at the very least, a geriatric service and consultancy in every autonomous region, and that every hospital should have a geriatric evaluation team working alongside primary care specialists.

"Although autonomous communities [regions] vary, there is an increasing desire – from both a political standpoint as well as from health care professionals, to optimise resources. The current situation in Spain is not so different to that of other EU Member States," insists Rafael Rosell, Head of Oncology at the Germans Trias i Pujol Hospital in Badalona (Barcelona), and President of the International Lung Cancer Association. Rosell maintains that an elderly person who has been diagnosed with cancer has the right to be involved with his/her doctor in choosing the most suitable form of treatment, "… and I'm not referring solely to the 60- to 70-year-old age group, but also to individuals aged 80 years of age, even up to 100 years – a population that is growing and is in better health than in the past. Longevity is important and we should strive to give more years of life and a higher quality of life with each passing year."

Rosell also acknowledges that, more often than not, the elderly are insufficiently informed as to the seriousness of their condition because relatives prefer to hide such information from them. This is why elderly patients do not play an active role in cancer treatment, "they are simply unaware of what is going on." He points to a retrospective study on lung cancer in 70-year-old patients, published in the *Lancet*, which demonstrated that treatment can be just as effective in this age range as in younger patients.

"We must not forget," says Rosell, "that the elderly population in developed countries is on the increase, and that ageing in itself is not synonymous with disease – a view that is often subscribed to as an excuse."

During the first half of the twentieth century the number of people over the age of 65 quadrupled while the rest of the population only doubled in numbers; henceforth 25% of the population in Western society will be over 70.

"We must address the fact that the elderly need access to clinical trials – which are key to testing new cancer drugs," Rosell insists, "not just to improve the quality of life, but also to improve survival rates, and even find a cure."

This article was published in *El País* on Tuesday 8th May 2001, and is reprinted with permission. It was translated by Amanda Wren.

THE ACE REPORTER AWARD

Getting the media on-message

The media shapes people's ideas about cancer. It can trumpet messages of false hope and spread dangerous scare stories. But it can also give accurate information about risk factors and how to minimise them, symptoms and how to check for them, treatments and what to expect from them, services – examples of best practice, exposures of shortcomings.

The ACE (Awarding Excellence in Cancer) Reporter Award was launched two years ago to promote accurate and informative coverage of cancer-related issues in the printed press. The award, which is worth 10,000 euros, is an initiative of the European School of Oncology in collaboration with Eli Lilly.

Have you come across any articles you felt were particularly effective?
Do you know of any journalists who have consistently helped raise the profile and understanding of cancer among the general public?
If you wish to make a nomination for next year's ACE reporter award, please contact Paul George at p.george@cprworldwide.com

Tailor-made vaccine hailed as milestone in renal-cell cancer

Janet Fricker

A new vaccine obtained from the patient's own tumour tissue may offer the first effective adjuvant treatment for renal-cell carcinoma following surgery. The findings of the phase III clinical trial are being hailed as a breakthrough in immunology therapy.

A recent phase III study suggests that a novel autologous tumour-based vaccine could reduce disease recurrences in patients who have had surgery for renal-cell carcinoma (RCC). The results, published in the *Lancet* (2004; 363:594–559) show that the new tumour vaccine lowers the relative risk of metastases and/or relapse in RCC patients by approximately 30% and thereby may prolong their life expectancy. The German study is being hailed as a 'milestone', since it could "serve as a concrete step towards making adjuvant treatment of renal cancer a routine and effective intervention."

Professor Dieter Jocham, the study's principal investigator, says his results are some of the first to show the benefits of any autologous tumour vaccine

The study's principal investigator, Professor Dieter Jocham of the University of Lübeck Medical School, Germany, is very excited about the results. "The significance of this study is that it's the first ever to demonstrate the benefits of additive therapy for patients with RCC who don't have metastasis, following surgery," he said. "It's also one of the first randomised controlled trials showing benefits for any autologous tumour vaccine."

RCC accounts for 2–3% of all malignancies, with the highest incidence occurring in the sixth decade of life. Of these, 70% are clear-cell tumours; less common cell types include papillary, chromophobe, and Bellini duct (collecting duct) tumours.

The tumour occurs in both sporadic and hereditary forms (the latter accounting for approximately 10% of cases). In sporadic forms, spontaneous mutations have been found on chromosome 3. Smoking and obesity are both risk factors implicated in its development. Other risk factors include exposure to cadmium or asbestos, and long-term intake of diuretics. End-stage renal disease has also been associated with an increased risk of RCC, arising from acquired renal cysts.

Professor Jocham adds pollution as a probable candidate for addition to this list of risk factors. "The incidence of RCC in the Western world is rising by 2–3% each year, and it's likely that environmental pollutants contribute to this increase, although definite causes have yet to be identified," he said.

Treatment options

Removal of all or part of the kidney (nephrectomy) remains the standard treatment for renal cancer. A radical nephrectomy involves perifascial resection of the kidney, perirenal fat, regional lymph nodes and ipsilateral adrenal gland. Lymph node dissection may not be therapeutic, but provides prognostic information, since virtually all patients with nodal involvement subsequently relapse with distant metastases, despite lymphadenectomy.

Nephron-sparing surgery is indicated in clinical situations where a radical nephrectomy would result in patients requiring dialysis. Nephron-sparing surgery is now becoming more widely

used in patients with small accessible tumours with a normal contralateral kidney function. "There's an increasing trend for patients with unifocal RCC tumours less than 4 cm in diameter to be considered candidates for partial nephrectomy, depending on the location of the tumour," said Professor Jocham. "Tumours on the outer surface of the kidney are considered more suitable than those in a central location."

So far, however, no effective adjuvant treatments following surgery have been established for this disease. In studies, various adjuvant protocols – including radiotherapy, interferon alpha, interleukin-2, and medroxyprogesterone acetate – have failed to show promise. "There have been around ten such randomised studies published in the past 20 years, and none could demonstrate a benefit for the patient – defined as improved progression-free survival and/or overall survival," said Professor Jocham, adding, however, that some drugs have been shown to be effective in patients with metastatic disease.

Observation remains the standard care following nephrectomy, with patients being offered abdominal CT scans four to six months after surgery to serve as a base-line. The lack of adjuvant treatment to reduce the likelihood of suffering relapse can leave many RCC patients feeling vulnerable. The relative five-year survival of patients with RCC for all tumour stages is 62%. After radical nephrectomy, 20–30% of patients with localised tumours relapse, with lung metastasis representing the most common site of distant recurrence. Most relapses occur within three years, and the two-year and five-year survival rates of patients with metastatic RCC are less than 20% and 5%, respectively.

Against such limited options, it is understandable that the new adjuvant approach, administering a non-toxic autologous tumour-derived vaccine, is causing considerable excitement.

TAILOR-MADE VACCINE

There are three main categories of cancer vaccine. First there are non-specific immunostimulants such as BCG, interleukin-2, and interferon alpha, which boost levels of activity in the immune system to reverse immunosuppression induced by the tumour. Then there are specific target vaccines that exploit the fact that tumour cells often express different antigens from normal cells, enabling the body to identify as foreign many antigens that occur particularly in malignant tumours.

The trouble is that antigens found in RCC tumours tend to vary from one individual to another, and no specific antigens have yet been defined that are found in all tumours. LipoNova, a biotechnology company based in Hannover, Germany, has therefore developed a 'tailor-made' approach, where vaccine is extracted from each patient's specific tumour material. The autologous vaccine has the advantage that tumour antigens are matched precisely to the patient, with inactivated whole cancer cells containing the entire spectrum of tumour antigens.

"The basic idea behind the vaccine was that each patient's tumour material differs slightly, and therefore the autologous vaccine made from the patient's own tumour tissue might be effectively administered to the person it was derived from, helping the individual immune system fight the disease," explained Jutta Ulbrich, Head of Communications, at LipoNova.

The procedure is as follows. First, the surgeon harvests a 10-g specimen from the peripheral zone of the tumour and places it in a tissue culture medium to be transported to LipoNova's laboratory in Hannover. Here, vaccine production includes in vitro incubation with interferon alpha to increase the antigenicity of the cells, and the addition of tocopherol acetate to protect inner and outer cell membranes during the incubation process. The cancer cells are killed by a devitalisation process involving repeated rapid freezing at -82°C and thawing, without a cryoprotector. Finally, washing procedures remove the interferon alpha, and the result is a pure autologous cell lysate vaccine, with no additional cytokines or bacterial or viral adjuvants present in the injected material. From start to finish, vaccine production takes between four and six weeks.

Professor Jocham and colleagues recruited 558 patients, aged between 18 and 70, who had been diagnosed with a renal tumour and were scheduled for nephrectomy. They were drawn from 55 medical centres throughout Germany, between January 1997 and September 1998. Before surgery, all patients were randomised to receive autologous renal tumour cell vaccine or no additional treatment (the control group). Patients, surgeons and other hospital staff were only told the outcome of randomisation after the surgical procedures had been completed. Ultimately, only 379 patients fulfilled the postoperative inclusion criteria for the study, which was a histologically proven RCC of stage pT2-3b pNO-3 MO.

Administration of the intradermal vaccine usually starts four weeks after surgery. Patients are given six intradermal applications of the vaccine into their upper arms at four-week intervals. They are then evaluated every six months for at least 4.5 years. The primary endpoint of the study was to

reduce the risk of tumour progression, defined by local recurrence or distant metastasis, confirmed by physical examination and/or imaging, or death. Measures of secondary outcomes included the effect of the vaccine on quality of life (to be reported separately) the success of the vaccine production process (total number of tumour cells) and the rate of adverse events.

Effects and side-effects

In the *Lancet* paper, Professor Jocham and co-workers report that the autologous renal tumour cell vaccine improved progression-free survival at five years from 67.8% in the control group (no adjuvant treatment) to 77.4% in the vaccine group. And with time, the benefits for treated patients became even more evident. At 70 months, the figures were 59.3% for the control group, compared with 72% in the vaccine group.

The final results reveal especially prominent differences for patients who are at increased risk of relapse due to their advanced tumour stage (large tumour size, high tumour grade or high Störkel scores). Relapse or metastases were detected over five years in only 32.5% of patients treated with the tumour vaccine, compared to 50.3% in the control group. The investigators add that it is noteworthy that only 12 vaccine-related adverse events were recorded in the study, and these were mild to moderate in severity. They conclude: "According to our results, application of an autologous renal tumour cell vaccine can be considered in patients undergoing radical nephrectomy due to organ-confined renal-cell carcinoma of more than 2.5 cm in diameter."

Since randomisation occurred before surgery, many patients had subsequently to be excluded from the study when histological and postoperative staging results showed that they did not fulfil the inclusion criteria. One criticism levelled at the study is that losing such a large number of patients (32%) after randomisation could lead to an imbalance in the two arms. "The prognostic features tabulated by Jocham and colleagues show that the number of T3 [stage 3 – 1993 TNM classification] subjects are about equal in the two groups, with most of the imbalance in the T2 subset. Although intuitively reassuring for the validity of T3 subset analyses, this finding does not fully compensate for the post randomisation losses," write Mayer Fishman and Scott Antonia from the H Lee Moffitt Cancer Center and Research Institute, Tampa, Florida, in an accompanying Commentary (p 583).

There are also concerns about the choice of progression-free survival as the primary end point, because other adjuvant approaches that have also shown an effect on progression-free survival have been rejected for failing to show an effect on overall survival. The authors say that they chose progression-free survival "because even with surgery for metastatic disease and modern immunotherapy …survival for most patients is between 12 and 18 months, and fewer than 5% survive longer than five years."

They add that since many patients with metastatic RCC enter clinical trials with different combinations of therapeutic approaches, this could vary the effect of the vaccine on individual outcomes, which could complicate the results.

Fishman and Antonia also comment that, since about a third of renal cancers occur after the age of 70 years, using over 70 as the patient age group might have been more appropriate. Professor Jocham agrees that this would be more representative of patients with RCC, but adds that they only recruited patients younger than 70 in accordance with the Helsinki rules of good clinical practice that applied at the time. "These rules have since changed for oncology, and in any future trials we would plan to include older patients," he said.

Despite their reservations, Fishman and Antonia hail the study as an 'immunological breakthrough', and conclude that "the carefully collected data are part of a broadening base of clinical observations of the potential to affect the biology of a solid tumour with non-toxic readministration of autologous tumour-derived material."

While we're waiting...

LipoNova submitted its Marketing Authorisation Application for the vaccine to the European Medicines Agency (EMEA) in December 2003. They hope to obtain the authorisation in 2005, after which they plan to make the vaccine widely available to all patients who would benefit from it.

"We are currently in the difficult situation where, on the one hand we have an obligation to inform patients about the results of the trial, but on the other insurance companies will only reimburse the costs of the treatment after the drug has been officially authorised," said Professor Jocham.

As the autologous vaccine is tailored to the patient's own tumour, it can only be obtained using samples of the patient's tumour tissue, which could be a problem if tissue removed at surgery is destroyed in line with common practice. LipoNova has therefore set up a tissue bank where RCC tumour tissue, removed at surgery, can be stored at no cost to the patient. This ensures that patients operated before the vaccine has been licensed will still have the possibility of being treated at a later date.

Talk to me not to your feet

What do patients have a right to expect from their oncologists? *Cancer World* asked glioma patient **Ivan Noble** for his views, after he issued a public *Plea to the Medics* in his widely read Tumour Diary column for BBC News Online, which is printed overleaf.

"The number one thing any patient wants from their oncologist is for them to be good at oncology. When I wrote *A Plea to the Medics*, I said 'Maybe I'm asking for jam,' to make the point that I haven't lost my priorities. It's not the most important thing, having a good conversation with my doctor. But it is important. It does affect not just the rest of my day, but the whole month.

My experience has been very mixed. The surgeon who conducted my initial biopsy was a fantastic communicator. After a week of progressively worsening headaches, I'd just found out through a CT scan that I had a 'space occupying lesion' on my brain. He told me who he was, what he was doing, why he was doing it in the middle of the night on a Bank Holiday Saturday, what he hoped to find, what he might find if it wasn't what he hoped, and what were the alternatives. Or as he said: "There are no alternatives to this procedure, so that's why we want to press on with it now."

He finished the operation at about 5.00 am. Four hours later he was by my bedside telling me what he'd found. "I'm afraid I didn't find what I'd hoped, and you've probably got some sort of a tumour, but it takes four days to get results on the stuff we've taken out. You'll find out then exactly what we can do."

He added: "We call them brain tumours not cancer. If you say cancer to people they think they will be dead in three months – and you won't be. Whatever happens, there is an awful lot we can do."

That last bit was just what I wanted to hear.

It was such a contrast, four days later. A registrar, about my age, was assigned to deliver the diagnosis, and he did all the things you shouldn't. He stared at his feet, and came out with something bizarre like: "There aren't any good brain tumours, but if there were, yours wouldn't be one of them." I couldn't make out what he was saying, though I knew it was really bad. He called it a high-grade glioma, stage III or IV. My wife said: 'Well, which is it?' And he said: 'It's a IV.' Then he said: 'Can I leave this with you, nurse?' And off he went. Shortly after that they told me I was going home. I had no idea what was going on. Do you mean going home to die? Or what?

I wanted to know what the doctors could do to help. I know you can't cure a glioma, but that is not something you should be ashamed of or

I had no idea what was going on.

Do you mean going home to die?

stand staring at your feet. You are a doctor. You can extend my life. You can improve my life. You can do something. So, tell me what you can do for me, and let's get cracking.

Doctors face a very difficult task when they decide how much to tell patients. They have to think about keeping a patient's spirits up and preserving the will to live, but at the same time depriving a patient of accurate information about their condition deprives them of the right to make well-informed decisions.

For my own part, I don't want anyone to sit me down and tell me that the median survival for patients with my kind of tumour is 9–12 months. That has nothing to do with me. It is a statistic that only makes sense when you are talking about hundreds of patients. And yet many oncologists seem to feel a responsibility to tell you certain facts, whether you want to hear them or not. Doctors are skilled technicians, not gods. They can't tell whether I will drop dead in two weeks or in 18 years. Statistics are useful for research and policy making – you can't use them to tell someone how long they are likely to live.

I do want to know as much as necessary when there is a decision to be made. You definitely want to be part of it. This year I had to decide whether or not I wanted a second craniotomy. Then I was happy to have a conversation. But once we've decided on a certain course of treatment, I say: 'Fine, let's crack on with it'. Until we get to a problem. Then we have to think of something else.

Everybody is different – that's the thing about people. So you can't write a formula and say this is the be all and end all of patient communication. Anybody with a degree of personal skills will sense how much a patient wants to know – and if they can't, then how about asking? Asking the patient to tell you how much they already know about their situation can be a good way to break the ice and give the doctor some idea of the level to pitch the conversation. It also makes patient feel listened to.

I never asked my oncologist – is this disease incurable? And he's never said. I don't know how deliberately he manages how much he tells me about my tumour, but I feel it has been about right, and his brisk confident manner usually makes me feel better.

Some doctors have this knack and others don't. Obviously experience plays a big role, but I have come across very young doctors who have completely mastered it. I think it boils down to being able to put yourself into the patient's shoes. If doctors talked to their patients more, they would find out more about them. And sometimes it would be nice to feel that they knew me a bit better.

IVAN NOBLE'S TUMOUR DIARY: 14 JULY 2004

A plea to the medics

We now have only a day to go until our son is due to be born. All being well, he should make his move some time in the next two weeks.

What with a pregnancy, two major brain operations and ongoing treatment of my tumour, we have had plenty of experience of dealing with the medical profession over the last nine months.

I have written before about my admiration for doctors' skill and persistence, so I hope I am not too far out of line now deciding to suggest a few improvements some of them might make.

First of all, the problem of delivering bad news. No-one likes delivering bad news. I know that I am not the first person to write this, but the shoe problem still needs dealing with. When delivering bad news, a doctor really should be looking the patient in the eye, not staring at his or her feet. Bad news is bad news, but I would have felt much less distressed when I was given my diagnosis had the doctor concerned spent a little more time explaining what was going to happen to me next and what could be done to help me.

As it was I left hospital in total shock and only slowly began to piece together what my treatment would mean. The doctor who gave me my diagnosis could not wait to get out of the room and hand me over to a nurse. Looking back now over almost two years, I have dealt with several shocks and I can put things into perspective now. But back at the beginning a little more time and a few more strong, encouraging words would have made that first week so much less painful.

I assume some doctors must feel a sense of failure when they give bad news to a patient. But there has to be another way of looking at it. Whatever the prognosis, there is always some way forward, even if the treatment is palliative rather than curative. And I know from personal experience that when someone did stand in front of me and tell me in a confident tone how my treatment was going to go forward, I felt a whole lot better.

WHO ARE YOU?

It is easy for doctors to lose sight of what it is like to be a patient. Doctors are part of a system which they understand. Patients frequently do not understand what is going on. If I go to a new place, I never do. It takes less than a minute to say to a patient "I am Dr So-and-so. I am a specialist in dealing with X. I am here to help you with Y problem. Dr Whatsit is the doctor who sent you to me."

Doctors dress in a much friendlier way these days, but that does lead to situations where if the doctor does not identify herself as such, no-one is the wiser. And terms like SHO and Registrar do not help people who do not habitually hang around hospitals. When someone says 'Registrar' to me, I think of 'Births, Marriages and Deaths'.

WHO AM I?

Patients like to think the doctor knows who they are. Obviously very few doctors can remember all their patients in detail – this is why they have notes. But it really does make a difference to the psychological impact a doctor's care makes on a patient if, before the patient gets through the door, the doctor has scanned through enough of the notes to know what the patient was last seen for and when.

And when patients are nearly always seen by a different doctor each time they come in, there has to be something that can be done to improve continuity. It really is quite disconcerting to go with your partner to an ante-natal check up and to realise that the doctor appears either not to have had time to read the semi-legible notes or not to be able to make sense of what the last person wrote. The overall impression is of being in a system that expanded by evolution, not design.

That is of course inevitable in such a massive and long standing institution as the health service. But there has to be time to look at some things and ask whether they are done for the benefit of patients, administrative convenience or after all this time, no-one at all.

Maybe it seems as if I am asking for jam on it when I know I live in a developed country where good care is mostly free. But I know I am not the only person who believes happier patients live longer and recuperate faster.

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Britain's Cancer Czar

Peter McIntyre

Five years ago, Britain's Prime Minister, Tony Blair, put out a call for someone who could get a grip on cancer services and pull up standards across the country. Oncologist Mike Richards agreed to take on the challenge. His progress is being closely followed in the rest of Europe.

The Minister left his desk with its picture postcard view of the Thames in central London and joined his team of civil servants on easy chairs around a table. An outer circle of advisers perched on straight-backed chairs. It was a stunning day but nobody was looking at the view.

John Reid, Secretary of State for Health in the Tony Blair Government, was being briefed about a harmless looking Parliamentary question from a Member of Parliament for Bolton. "How many additional scanners have been provided in the NHS in the last year, and how many of these are in the north-west?"

In the world of Westminster politics this was an opportunity for the Minister to highlight extra money spent on cancer services, and a potential trap, from behind which the Conservative opposition might launch an ambush.

John Reid, famous for his somewhat gruff Scottish public persona, was not happy with the draft answer, because it did not say where the scanners came from. He told his civil servants: "They do not just appear from nowhere. It was our decision to provide them."

The Minister was concerned about where opposition politicians may direct follow-up questions. He wanted facts to rebut attacks, not apple-pie answers about doing everything possible, he growled, with a humorous aside about the loneliness of a Minister at the dispatch box.

However, he listened closely as an adviser explained about the problems of success. Far more people in the UK are receiving treatment for cancer than ever before. And as family doctors refer more patients for hospital tests (another success), the waiting time before receiving a diagnosis has risen in some areas. So too has the wait for radiotherapy treatment.

This adviser was not a civil servant, but Professor Mike Richards, medical oncologist and specialist in palliative care, from across Westminster Bridge at St Thomas's Hospital. He is the man Tony Blair appointed to transform services at a time when the UK was propping up European league tables. His official title is National Cancer Director, but he is better known as Britain's 'cancer Czar'.

Richards has learned to live with this title, although its suggestions of dictatorial power sit awkwardly on a courteous man who likes to

listen. "It is not a title I would use, but if it raises the profile of the work and helps to get the job done then I do not object. My post reflects the fact that cancer is being given priority.
"I have what authority I have because Ministers have given it to me. My job would be impossible if I did not have their support. Equally it is very important that I am seen as independent. I also work with clinicians in the broadest sense of the word – doctors, nurses, professional groups, charities, patient groups, chief executives… a whole range of stakeholders in the cancer world."
Whether the title helped or not, the UK is doing something right. Cancer death rates in England are falling faster than in most of Europe. However, this is progress from a very poor beginning. And with 225,000 cases of cancer each year in England alone and 120,000 people dying from the disease, cancer remains one of the biggest health challenges.

The road to Czardom

In 1993 Richards became director of clinical services at Guy's and St Thomas' Hospital. He helped to develop a cancer network covering a large area of south London, improving links and communications between the General Practitioner family doctors (GPs) and the hospital specialists. Such networks are now a key part of the NHS (National Health Service) Cancer Plan for England.
In 1995 he was appointed as Sainsbury Professor of Palliative Medicine at Guy's, Kings and St Thomas' Hospital School of Medicine, focusing on pain relief and quality of life for patients whose cancers were not going to be cured. He continued to treat patients as a medical oncologist.
While Richards was happy in his work, he was nagged by a growing sense of unease about the overall quality of cancer care in the country. He remembers a phone call from another hospital where a colleague wanted advice about how to treat a patient following surgery for breast cancer. How big was the tumour? "We don't record the size of the tumour." Had the cancer spread to the lymph nodes? "In this hospital surgeons do not remove the lymph glands," came the reply.
After more fruitless questions Richards realised that he could not give his colleague any useful advice, except to change the policies of his hospital. "As a clinician I was able to treat a couple of hundred patients a year and I believe I was able to treat them very well, and that did give me a lot of satisfaction. But what about thousands of other patients who were getting sub-standard treatment?"
This was a question he was soon asked by the Prime Minister, who came to power in 1997 with a commitment to improve the performance of the NHS. By the late 1990s, results of the Eurocare 2 study were being assimilated. The high-flyers were Sweden, The Netherlands, France and Switzerland. The poorest results were from Estonia, Poland, Slovakia and Slovenia. Survival in England was classified as low for lung, breast, stomach, bowel and prostate cancers.
In 1999 the London School of Hygiene and Tropical Medicine and the Office for National Statistics published a study of cancer survival trends in England and Wales.
- Survival in England and Wales was lower than in comparable countries in Europe,
- There had been little or no progress for several lethal cancers in adults in 25 years,
- Thousands of cancer deaths were avoidable, and
- Poor people got cancer more often, and once they had it they died from it faster.

By now politicians had become alarmed. Was the UK really competing with Estonia at the bottom of European league tables?
Tony Blair called Richards to Downing Street and asked five questions. Was the situation as bad as the figures suggested? Why was it so bad? What would he do to change it? How long would it take? How much would it cost?

Was the UK really competing with Estonia at the bottom of European league tables?

As National Cancer Director, Mike Richards, based at St Thomas's on the South Bank, provides a bridge between the world of cancer care and the world of politics across the river

The Plan seeks to bring care in every part of the country up to the standard of the best

Whatever Richards said must have sounded convincing. In October 1999 he was appointed as National Cancer Director.

Where do you start on a plan to deliver measurable improvements and set achievable targets for reducing cancer deaths?

Richards says: "We convened a workshop of experts to look at the big studies that compare England with European countries, and in particular the Eurocare study. It was vital to know how much reliance I could put on that data, and the answer resoundingly was that this was very largely fact, not artefact. That was very important."

"The first year of my task was taken up with what needed to be done across the board from prevention through to palliative care." In some areas Richards knew the shape of the reforms that he wanted. In others he relied on colleagues. "Did I know exactly what needed to be done on smoking? No, I am not an expert on that. Nor was I an expert about diet and fruit and vegetables and on screening etc., although I am more of an expert now than I was."

There was a need for a cultural shift – for the public to fear cancer less and to act more quickly, for GPs to speed up referrals and for hospitals to improve their response. There was also a need for resources if the NHS was going to deliver on its promises.

The Plan

The NHS Cancer Plan seeks to reduce three significant delays. The first is the delay between the time someone has symptoms and the time they

seek medical advice. Some women delay a visit to their GP after finding a lump in their breast because they don't want to have their fears confirmed. Many people with advanced lung cancer simply have no idea, despite symptoms, that they are seriously ill, which is one reason why survival rates are so poor.

The second delay is in referring the right patients for the right tests at the right hospital. GPs see thousands of patients a year of whom only a few have cancer. Referral guidelines for GPs are currently being updated.

Third comes the delay in diagnosis and treatment once a patient is referred to hospital. The aim is that a patient should be seen at hospital within two weeks of an urgent referral, and that treatment should start no more than 31 days after diagnosis.

The Plan is about more than speeding up the process. It seeks to bring care in every part of the country up to the standard of the best. A system of 34 local cancer networks now covers the country, so that professionals in the community, local hospitals, cancer centres and hospices refer more accurately across organisational boundaries. Service improvement teams have been appointed to work with 1,600 specialist cancer teams in England to improve care through peer review.

Richards says: "That is one area where we will soon be able to say we are in the lead: 80% of patients are now seen by multidisciplinary teams, and that is higher than in America and in most other countries."

The National Institute for Clinical Excellence (NICE) has reviewed most of the major cancer areas and issued guidelines for diagnosis and care. Under the NHS, local Primary Care and Hospital Trusts have autonomy on how they commission services, and there is no guarantee that NICE guidelines will be implemented everywhere, especially when they recommend expensive treatments. However, Ministers have made it clear that they expect those commissioning health services to act promptly on advice from this authoritative source.

Cancer services now attract an extra £570 million (830 million euros) a year from central funding, which allows real progress in commissioning equipment and recruiting staff. Richards emphasises that change on this scale involves a long-term commitment by Government and at every level in the NHS.

"The NHS is one of the largest organisations in the world. It has 1.3 million people working for it. Whether it is bigger or smaller than the Chinese Red Army or the Indian railways I am not sure, but they always get compared. It is a constant challenge to make sure that communications get through.

"We have a relatively small full-time workforce of 10,000 to 15,000 oncologists, palliative care specialists and specialist nurses who deal with virtually nothing but cancer. There are a whole lot more for whom cancer is an important part of their working life: the chest physician who specialises in lung cancer, the colorectal surgeon who specialises in colorectal cancer. Then there are hundreds of thousands for whom cancer is a small part of their working life, including 30,000 GPs and 30,000 High Street chemists who may dispense hormone tablets to women with breast cancer.

"My post is about making sure the Plan does happen in all these areas. It is partly about winning hearts and minds, about communicating to those out in the NHS what the Minister thinks and about communicating back to Ministers what the NHS is thinking."

Richards seizes every opportunity to talk and listen to staff. He was due to open a new cancer unit in Ipswich. "There will be a lot of jollifications, but the value of my going is I will hear from people on the ground. Apart from cutting a ribbon it gives me the opportunity to hear from

Change on this scale involves a long-term commitment by Government and every level in the NHS

consultants, senior managers and from radiographers and nurses. It is important that I keep myself grounded."

Amongst his most challenging experiences was addressing 450 teenagers who had survived cancer. They used keypad voting to prioritise their questions and each had a drum to indicate what they thought of the answers. A loud drum burst indicated approval; a single drum beat, boredom. "I can assure you they did not give me an easy time. They could give me instant feedback on what they thought of my answers."

Four years after the plan was published, his verdict is positive. "I have no doubt that we are making progress, whether on smoking prevalence, improving our screening programmes, cancer services in the community, improving services in hospitals or supportive palliative care services. If you look at the number of scanners and radiotherapy machines, all of these are going in the right direction faster than we have ever gone before. However, there is a huge amount more to be done before we have got the cancer services that the population deserves."

He acknowledges that targets can be a blunt instrument, but believes that these targets reflect clinical priorities.

"If the targets describe something important both from the patients' point of view and from the doctors' point of view, then having a target can be useful in focusing the efforts of everybody down the scale – from Ministers, Czars and chief executives to people in individual departments. We know that cancer waiting times have a very high importance to the public. If we are aiming to be a high-quality service, then these things matter.

"People have known about the targets for four years and have not questioned them, but they may start questioning them now that they are being forced to implement them. But everybody

BLUEPRINT FOR BETTER SERVICES

THE PLAN

The NHS Cancer Plan, published in September 2000, pledged to reduce cancer death rates in people under the age of 75 by one fifth over a 14-year period. The Plan also aims to reduce inequalities and promises a greater investment in recruiting and training staff and in equipment. It covers everything from primary prevention to detection and screening, diagnosis, treatment and palliative care.

TASKFORCE

A national Cancer Taskforce was established to drive the Plan and advisory groups have been established for individual cancers. They include GPs, hospital specialists, nurse specialists, managers, voluntary groups and patient representatives.

LIVING WITH CANCER

In a bid to improve care for people living with cancer, a National Partnership Group for Palliative Care and a Coalition for Cancer Information were set up. The National Cancer Research Institute was set up in 2001 to aid collaboration and identify gaps in research.

SCREENING

Four years into the Plan, the national breast screening service has been extended to include women aged 65–70. The cervical screening programme, which has reduced mortality in women under the age of 75 from 8 to 2 deaths per 100,000, is introducing liquid-based cytology to improve the quality of smear slides. A national screening programme of adults over the age of 50 will be introduced to detect early signs of bowel cancer. An appraisal is under way to decide between the faecal occult blood test and flexible sigmoidoscopy. A national screening programme will not be introduced for prostate cancer, but PSA tests are being more widely advertised and offered.

REFERRALS

Today, more than 98% of patients who are referred urgently are seen by a specialist within two weeks, while almost 97% of women with breast cancer receive treatment within a month of diagnosis.

PALLIATIVE CARE

The Plan also includes improvements for people living with cancer, with a review of care guidelines by the UK National Institute of Clinical Excellence and £50 million for specialist palliative care.

The NHS Cancer Plan is at: *www.publications.doh.gov.uk/cancer*
The three-year progress report, *Maintaining the Momentum*, is at: *www.dh.gov.uk/assetRoot/04/06/64/40/04066440.pdf*
The plan covers England alone, as Scotland and Wales run their own health services while Northern Ireland has its health service run directly from Westminster. Wales has a target to reduce cancer deaths by 20% by 2012. Scotland has its own strategy *Cancer in Scotland: Action for Change*, published in July 2001.

has been saying these are sensible targets and they are reasonable."

It will be some years before European studies show the full impact of the Plan. But the latest figures show a rapid fall in cancer deaths in England and Wales, especially in lung cancer in men and breast cancer deaths in women. A three-year progress report of the Cancer Plan, published in October 2003, showed that the overall cancer death rate had fallen by 10.3%, ahead of schedule for the 20% target by 2010.

Richards acknowledges that much of this is due to a reduction in smoking. "This began before I ever came on the scene. The test for what we are doing is can we now accelerate?"

are trying to do in 14 years what they did in 19. The question is: Can we go faster?

"We were amongst the first to have a Plan. A lot of other countries are looking at how we have gone about that and whether that would be useful for them. There is recognition that to get the maximum benefit, it is the comprehensive nature of looking at everything from prevention through diagnosis, treatment and care that matters."

When progress was reviewed in October 2003 there was a very positive reaction from professionals and from patient organisations. Peter Cardy, Chief Executive of Macmillan Cancer Relief, said the plan was making a real difference to the patient experience. "There are some great

Because more affluent areas are also improving, it is proving difficult to close the gap

The UK has not yet shown the boldness of the Republic of Ireland in banning smoking in workplaces – including pubs. Moreover, Tony Blair's Government had its anti-smoking credentials dented soon after coming to power when it exempted Formula 1 Racing from a tobacco advertising ban, shortly after the Labour Party had taken receipt of a £1 million donation from the man who controls the sport.

The Plan does, however, include initiatives on smoking, diet and exercise directed particularly at areas of deprivation. The Public Health Minister, Melanie Johnson, chairs an inequalities group within the Department of Health focused on speeding up improvements in 73 Primary Care Trusts (PCTs) in deprived areas, and has set a target of reducing inequalities by 6%. But because PCTs in more affluent areas are also improving, it is proving difficult to close the gap.

Playing catch-up

Richards visited many countries to see what the UK can learn and concluded that those with most success, such as Sweden and Finland, simply started doing the right things sooner. "I firmly believe that the targets are achievable, but we

initiatives such as user involvement, cancer leads [team leaders] in every primary care organisation and cancer networks that are really shaping future cancer services. We must ensure funding to continue these initiatives gets to the frontline."

A few days after his briefing, the Secretary of State told the Member of Parliament for Bolton South East that 29 CT and 16 MRI scanners were delivered to the NHS through centrally funded programmes in 2003–2004, of which six went to the north-west. The number of clinical radiologists had increased by 26% and diagnostic radiographers by 13%. There was no ambush, but his colleague Melanie Johnson was asked why waiting times for radiotherapy for breast cancer patients had risen in one area.

She responded: "To a degree we are victims of our own success: as a lot more women are identified, a lot more women need treatment." She also said that she had asked the national cancer director to look into the issue.

Another task for Professor Mike Richards and his team. The English patient seems to be responding to treatment but there is still much recovery to be made. It looks as though the NHS will have to keep taking the medicine.