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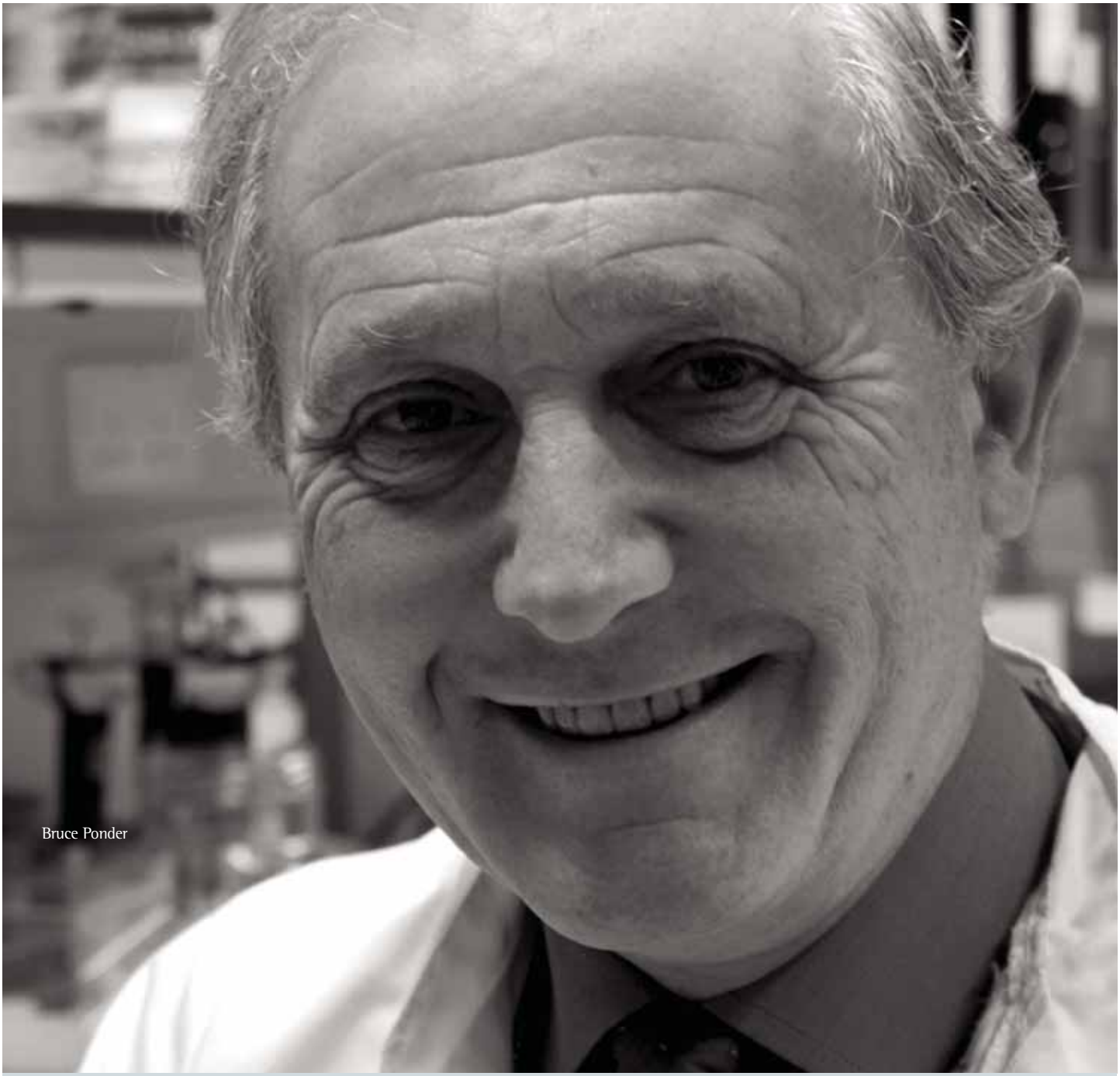

Bruce Ponder

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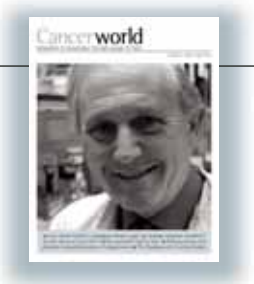

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Direttore responsabile
Emanuele Bevilacqua

All enquiries about *Cancer World* should be made to:
ESO Editorial Office
Viale Beatrice D'Este 37
20122 Milan, Italy
e-mail: magazine@esoncology.org
Fax: +39 02 8546 4545

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The power of words

Kathy Redmond ■ EDITOR

Blogging – a novel form of Internet communication – is starting to enter the cancer world. A 'blogger' is someone who posts their thoughts and opinions to an online journal (called a 'web log' or 'blog'). The best bloggers are insiders – people who can candidly describe a particular reality, warts and all.

Ivan Noble was a wonderful blogger. Tragically, he died last month after a two-year struggle with a high-grade glioma. His online diary, started soon after being diagnosed, charted his fight against a particularly aggressive cancer – his frustrations, fears and despair as well as hopes, dreams and joys. He wanted to use his ability as a technology reporter to help demystify the disease, but later he moved on to explore, with painful clarity, how to carry on living a full life in the face of enormous uncertainty.

E-mails flooded in from all over the world whenever he posted an entry. Many of them were published on the same page. Some people wanted to share their own cancer stories; others wanted to offer support or tell Ivan about the strength they took from his courage and tenacity. It was a dialogue of solidarity in the face of adversity. In acknowledging the painful reality of living with a life-threatening disease, Ivan prompted fellow cancer sufferers, their friends and families, to speak about their experiences – the positive and the harrowing. He helped people make sense of an unfathomable situation.

Ivan got a lot out of writing his diaries. He was determined to fight back against the powerlessness of his grim situation and make something good out of bad. He said he wanted to "prove that it was possible to survive and beat cancer and not to be crushed by it." Though he knew he was dying, he wrote "I feel I managed it. I have not been defeated." His diaries helped take Ivan out of himself and allowed him to retain a sense of continuity with his 'previous' life. He believed that the messages of support and insight he received from readers helped him survive for as long as he did.

Ivan Noble's Tumour Diary, and the responses it evoked, show the power of narration in helping people cope with a devastating life crisis. The cancer community owes Ivan a debt of gratitude for sharing so frankly and eloquently all the unpredictable ups and downs of his cancer journey.

Ivan's diaries can be viewed at BBC News Online (*www.bbc.co.uk*). A collection of his diary postings will be published later this year by Hodder

All correspondence should be sent to the Editor at editor@esoncology.org

Bruce Ponder: plugging the research gaps

Marc Beishon

"Just do it" is a lesson Bruce Ponder learnt early in his research career, and it has stood him in good stead. He is now director designate of one of Europe's largest cancer research centres, where he intends to plug many of the research gaps that the cancer community has been complaining about for so long.

IN conversation with Bruce Ponder, in his fairly unassuming office in the Hutchison/MRC Research Institute on the Addenbrooke's Hospital site in Cambridge, it takes a while to appreciate just what he is presiding over. Using his background in genetics, molecular biology and clinical oncology, his mission is to build what will possibly one day be the largest scientific cancer research centre in Europe.

It will comprise not just a new £40 million (58.2 million euro) translational research institute staffed by 300 researchers, but will bring together existing institutes such as the Hutchison/MRC – itself a very new facility that houses cancer cell research – and academic departments and clinical facilities in a 'virtual' cross-disciplinary effort.

That new translational facility, known at present as the Cambridge University/Hutchison/Cancer Research UK Institute, is a year away from occupation, and Ponder is its director designate, as well as being Professor and Head of the University of Cambridge/Addenbrooke's Oncology Department, and co-director of other institutes. It's a potentially confusing picture, but Ponder is absolutely clear about its aim.

"What I'm keen to do is ensure that, although there will be this new institute that will be funded and evaluated like any research facility of its type, there is additional funding that supports the clinical side, and that the two are judged together. It is the interface between research and the clinical side that is really important."

It is self-evident, perhaps, that creating the best pathways for new, effective clinical practice is always the priority. But as Ponder points out, despite the UK's reputation for research excellence, funding agencies have tended to treat research institutes and clinical departments as separate entities and "not looked at the interface between them as closely as they should."

In fact, until recently the UK has suffered many of the same structural and professional problems as other countries when it comes to research opportunities, best use of resources and career pathways. As recently as 2000, Ponder gave evidence to a parliamentary committee about the state of cancer research, in which he

RICHARD BAKER / IPG

"It seemed to me that if you want to specialise in cancer you need a strong scientific platform"

RICHARD BAKER / IPG

pulled no punches, especially about the lack of an adequate infrastructure for applied clinical research. As a result, many of the brightest graduates are going into basic medical research – and staying there.

Some of these criticisms have started to be addressed. The formation of a National Cancer Research Institute has been a big step, while Britain's National Health Service (NHS) is looking at how its own research budget is spent to better effect, for example, by creating a national cancer research network to support clinical trials and other research.

But there is still an awful lot to do, in Ponder's view, before the UK will see a streamlined system where cancer doctors are training and working on the right subjects at the right time and in the right places to maximise that scientific-medical interface.

His own career path is a case in point, especially in his early years, as he had to continually move around to find the backing and resources to work on promising research while also progressing his medical training.

At school, he horrified his teachers by switching from English and history to science, at a time "when it wasn't respectable for an academically minded boy to do biology – it was considered a soft subject." But the seeds had been sown earlier, when a primary schoolteacher had showed him how to look at pond life under an old microscope, and he also ran a school weather station for a year.

He went to Cambridge to read medicine – although he could equally have stuck to straight science – but "it was clear that medicine was an interesting and natural way to apply your knowledge." Although he could have stayed on as an academic, Ponder chose to begin a career as clinician, moving to St Thomas' Hospital in London, and "thoroughly enjoyed six or so years of clinical practice and training," doing the usual rotations in

various hospitals, and returning to St Thomas' to finish his general training in internal medicine.

"It was then I decided I really wanted to do research and go back into science – it seemed to me that if you wanted to specialise in something like cancer you needed a strong scientific platform, otherwise you wouldn't be equipped for the future."

Casting around at St Thomas' for a research topic and supervisor, he soon found that the teaching hospital didn't have anyone really informed about lab research. He was referred to the Imperial Cancer Research Fund – "They'll give you a tough project you won't understand" – and to an array of top researchers. Director Michael Stoker duly set him up with a fellowship to do a PhD on the structure of chromatin in polyoma virus, which led to a paper in *Cell*. "I had a fantastic time – probably the happiest three years I've had," says Ponder. "I went to get training in how to do science, not anything that was applied in a particular way." Certainly, the drive to carry out research seems to have sustained him ever since.

In any case, Ponder was already interested in cancer, as it had the attraction of covering a wide spectrum – from difficult palliative care issues all the way to understanding fundamental biology. "It had everything for me – I realised I couldn't do it all, but I knew I would end up somewhere on this spectrum." On a summer school in 1975 he met John Cairns and helped him write *Cancer, Science and Society* – a book for non-specialists that is still required reading on at least one course of the same name at Johns Hopkins University.

"I wanted then to train in clinical cancer medicine, but there really was no place suitable – Barts [St Bartholomew's, London] was then the leading UK centre, but specialised in leukaemia and lymphoma – and there wasn't much epithelial oncology." The Cancer Research Campaign awarded him the first Hamilton Fairley Fellowship to train abroad for a year at Harvard medical school, but although he found the experience really useful and liked the university, he stayed only for that year, as by this point he was married with four young children. "The Americans weren't sympathetic to anyone doing anything other than working – we had very little money and my wife was rather isolated there."

Back at Barts he worked as a senior registrar in oncology and, although he was soon to move much more into research and the genetics field, he considers that his experience on the clinical side has put him in a far better position to bridge the clinical–research science gap than someone trained only as a scientist – and of course today he also heads the university/hospital clinical oncology department.

"That taught me a lesson. Don't wait for someone to tell you what to do – just go and do it"

Determined to work on a sound scientific basis as an academic, and eschewing the chance to become an oncology consultant, Ponder went back to the Cancer Research Campaign and obtained a career development grant that took him to the Institute of Cancer Research in Sutton and his own programme researching the organisation of epithelia in chimaeric mice. "I wanted to study epithelial cancer and its biology and it seemed to me that cancer wasn't just a matter of disordered or excessive growth – more a problem of the breakdown of the rules that govern the organisation of tissue." The idea was to gain insight into the clonal structure of an epithelium and how it broke down in cancer.

"We didn't have the tools then to take it further. What we needed were inducible markers linked to a gene that you can also induce, then you could perturb particular gene expression in cells that are marked and see how that affects the behaviour of the clone. And that's what

we are doing in the lab here 20 years later. It is only now we have the technology to do it."

While at the Institute of Cancer Research, Ponder also held a clinical appointment at the next door Royal Marsden, a major UK cancer hospital, presenting himself as a free resource – but found his background as a molecular biologist failed to excite. "That taught me a lesson which I keep telling young people: Don't wait for someone to tell you what to do – just go and do it. The mistake I made was thinking that anyone more senior had the time to worry about what I needed to do."

The Ponder Lab, 1989

Casting around, he joined a group of urologists – identifying the bladder as a suitable organ to contribute to his research on epithelia and their clonal organisation. "No one was doing much medical oncology in that area then."

"That's where I learnt my second lesson: to collect all the samples and work with a clinical team requires a lot more time and resource than one person doing a lab project can possibly have – people constantly underestimate the resources needed to do decent clinical research."

Then came a 'strike of fate' that often changes a career – in Ponder's case, it was on a slow day in urology. Seeing that next door the thyroid clinic was very busy, he offered to help out. He found piles of case notes on the clinic table and took two of the thickest ones there. "They were two different families with inherited thyroid cancer – and while the cancer was being looked after, it was clear no one was really looking after the families. I'd read papers about Huntingdon's and how researchers were setting out to find the genes by linkage – so I thought to do the same with cancer genes by collecting thyroid families. It took me about five years to persuade anyone I was serious, but we did it."

He was told in no uncertain terms that while his work on bladder and also prostate cancer was very interesting, cancer genetics should be kept strictly as a hobby. "They thought there was no future in it. My colleagues said, 'This is a cancer hospital – we treat cancer patients here. What you appear to be interested in is people who haven't got cancer but who might get it. That doesn't belong in a hospital – you should be in some epidemiology institute.' The model for medical oncology then was restricted pretty much to chemotherapy – my approach just didn't fit."

Fortunately, Ponder was able to take over some posts not filled in another department, and he recruited a molecular biologist and also his own wife as a research nurse to collect families, "and we linked the gene [for thyroid cancer] and so no one could really say boo then."

It was crucial, says Ponder, to be based in the hospital and also to be trusted as a cancer doctor. GPs could be confident that if referrals revealed a raised risk (there was also a biochemical screening test), then the best advice and, if necessary, treatment – which could be a thyroidectomy – could be given.

With both his gene linkage and work on mice going well, Ponder needed to expand – and it was Cambridge that gave him the opportunity. "I thought I was going to find the (thyroid) gene I had done the linkage for and understand how it worked," he says. "I was also the Chair of the International Consortium for Breast Cancer Linkage at the time, and I thought we would repeat the process for that disease too." The work with mice would then help complete the picture by manipulating the genes in tissues to find out what the effects were.

Ponder's team found the RET gene implicated in thyroid cancer in 1993. "But doing the biology for RET turned out not to be easy for me, as the gene is a receptor tyrosine kinase – a member of a large family – and there were real experts in this around the world who could do in a week

what it would take me two years to do. So I couldn't make much more of a contribution in terms of what the gene did.

"But where we could make progress was relying on my clinical and genetic epidemiology expertise. Because we knew there were different clinical forms of the syndrome, we were able to sample large patient collections and demonstrate different mutations in the gene and different forms of the syndrome. That's commonplace now but was fairly novel then and gave useful insights."

Ponder's group was then able to help draw up new guidelines for management of the families with thyroid cancer – and by the mid-1990s was pleased to report that outcomes had improved over previous guidelines.

Work on breast and ovary cancer went forward in parallel, with Ponder's team contributing to the international effort to find linkages, contributing families to Mike Stratton's work on the BRCA2 breast cancer gene and making one of the first BRCA2 'knockout mice'. That biological work is ongoing at the Hutchison/MRC institute under one of Ponder's colleagues.

As he points out, the early work on identifying often rare familial syndromes has fuelled the more recent work on cancer mechanisms. "And in the current phase we have realised that those striking families are only a small part of the total amount of inherited susceptibility. Fewer than 5% of breast cancers are attributable to single strongly predisposing genes. However, there is a distribution of risk across the population which is determined by combinations of weaker genes. We've now shown that probably half of all breast cancers occur in about 12% of people at highest risk. In fact there is probably a 40-fold difference in risk between the top 20% and bottom 20%."

Although only a model – though a robust one, according to Ponder – the idea of a wide combination of genes contributing to the distribution of susceptibility has been difficult for many. "I think I'm a fairly good lecturer, but I have to cover this three or four times," he notes. "The idea of course is well established in the literature on the genetics of flies, for example – it's just that conventional molecular biologists aren't used to it. We have identified some of the variants but not many yet – it's a massive task."

As he continues: "We would like to understand how this genetic variation causes this predisposition. It's likely to be mutations on the direct pathway of the events that turn a normal cell into cancer cell, but the genetic variants that add to risk are more likely to influence things that impinge on this pathway from outside the cancer cell, and this may be a better set of targets for prevention."

> "People constantly underestimate the resources needed to do decent clinical research"

Ponder's view is also that early work should be targeted at those at highest risk even if they comprise a minority of the disease. "If you establish the principles that your intervention is successful you can then consider generalising it more widely."

Any cancer centre head wants to carve out a distinctive profile. Ponder says that on the science side, the focus for the new institute will be more on the environment of the cancer cell in the tissue, than events in the single cell. "Most other institutes focus on cell signalling pathways, cell cycle transcription and that sort of thing – very important but we are more interested in the interaction between cancer cells and surrounding normal cells."

Meanwhile, on the clinical side, Ponder says the aim is not to be another experimental cancer therapeutics base – other UK centres are focusing on drug development and on phase III work, for example, and he's happy with that. "We will do clinical trials but based on biological research –

Visiting labs in the University of Shantou, People's Republic of China, as part of a collaborative project on the genetics of nasopharyngeal carcinoma

early stage trials of agents which impact on pathways where we think we have particular scientific expertise." Genomics and molecular imaging expertise will also be developed further.

"We think too there is mileage in finding out how to use existing drugs better – by examining molecularly well-described cancers from the local population to get insights into the determinants of response and resistance."

In the longer term, Ponder wants to hone that focus on the early stage of cancer development as the most distinctive – and most difficult – contribution. "What I'm hoping is that the new institute will provide the reagents and tools to complement the genetic epidemiology and public health work we have at the Strangeways Research Lab," (another institute where he is co-director). This all means identifying higher risk groups, running screening programmes to identify early lesions – hopefully at some point from non-invasive imaging – and developing targets for intervention and markers of response.

It also means investment in a new cancer centre at Addenbrooke's with the equipment needed for early intensive investigations.

Ponder is pleased to note that more funding in the UK is earmarked for applied research – one of the initial moves is the establishment of a National Clinical Trials Network, with Cambridge one of the first regional centres. With extra resources for nurses, the clinical trials entry has gone from 2% to 14% of new patients in four or five years. Britain also has a National Translational Cancer Research Network (NTRAC) – again Cambridge is one of the participants.

However, too many trials are determined by funds from drug companies, says Ponder, who is concerned that more intellectually useful work is not being done. "For example on local trials we've thought of ourselves, or MRC [Medical Research Council] trials, the hospitals simply don't have the money to do them." This is one gap in his parliamentary submission that he feels is not being closed yet, but he says there is "general recognition that there is a problem."

"I have, though, persuaded Cancer Research UK to invest also in the clinical department on information systems, sample collection, pathology time and so on – above what we need for NHS service – to provide an environment where clinical research can happen."

Away from Cambridge, Ponder has made many visits to other scientific research centres – including assessment visits in Europe – and feels that some lack the 'buzz' to provide a stream of top-quality researchers. "I have a lot of recruitment to do here – including 10 professorial appointments – and in all the due diligence I do I just don't find many candidates from Europe," he says. "There are individually excellent people there but I don't get the sense that overall the centres compare with the best in the US and probably not with the best here."

If top scientific researchers are hard to come by – and more need to come from the UK as well – so too are top clinical academics, with expertise in the UK being spread too widely across too

"We've shown that probably half of all breast cancers occur in about 12% of people at highest risk"

Ponder feels it's not his place to be heavily involved in the ethical debate about genetic testing

many centres. "Many clinical academics have not had much scientific training – we are still inclined here to create new centres and professorial chairs for people who are undoubtedly good clinicians, but they do not really have the research background to sustain them." That has a knock-on effect with a lack of role models for the next generation, he feels.

Ponder would rather see a smaller number of cancer centres with some of these, often young, oncology professors dropping back to intermediate academic positions at a top quality institute, and "really getting 10 years of solid research under their belt."

He also feels oncology in the UK has been too focused on medical oncology and also radiotherapy (the latter being "academically quite weak"). "So it was quite deliberate that the first appointment I made here was a professor of cancer surgery – the delivery of cancer care and research is a combination of oncology, surgery, pathology and imaging – and we need leadership in all of those disciplines."

Again, there had been progress here, he notes, with Cancer Research UK taking on fellows in surgery and pathology as well as oncology. But there are currently relatively few professors of cancer surgery in the UK, he feels, and pathologists are particularly hard to find. He'd also like to see his own university teaching medical students more about cancer – there is only a few days on the topic, he says, and a presumption it will be covered in other organ-based sessions.

Until a recent submersion in all the administrative work of launching the new institute, Ponder was regularly seeing patients in the hospital's genetics department, sensitive always to the relationships between family members who may be present, and what they want out of the visit. As he says: "A relative may have dragooned them into it, or their family doctor may simply have thought it would interest me."

However, he feels it's not his place to be heavily involved in the ethical debate about genetic testing and the like. He has contributed to the government's Human Genetics Commission at a high level, but says that advocacy work should come from the patient side – and indeed his wife Maggie is the chair of a charity called the Genetic Interest Group, which acts for families with genetic illnesses.

"There is a danger of the tail wagging the dog – people with sincerely held views but on the whole obstructive of research," comments Ponder. "I think there is a large silent majority who wish they would go away – but that's much easier for patient representatives to say."

Ponder has the usual string of top awards with the stand-out being election to Britain's famous Royal Society. It's not been enough to tempt any of his children into medicine – although two are working as scientists. Home interests include walking, wine, golf (he's been a single handicap player for many years) and gardening – they grow vegetables and flowers and keep ducks and other animals. "It's all a bit of a shambles," (one suspects a lack of Linnaean order here).

That relaxation is understandable given what's on his plate at work – and he's got another seven years in post to build the research base that should be the rival of any centre, although of course an institute is there for the long term.

Despite the advances made in recent years, Ponder rattles off a long list of fundamental things we just don't know about cancer – how little we understand about gene expression, cell to cell and protein interactions, and cancer stem cells, for example. And why do barely one in a hundred drugs hit their targets and why do those that do work?

It's axiomatic of the field perhaps that wherever you are it feels like you've only just begun.

Treating anaemia: damned if you do, damned if you don't

Mary Rice

Many cancer patients suffer unnecessary levels of fatigue due to a failure to treat their anaemia. But just as the cost of erythropoiesis-stimulating proteins looks set to fall, surprise research results are prompting questions over whether these drugs might actually be stimulating tumour growth.

Until recently, epoetin, the human recombinant form of erythropoietin, was considered by most oncologists to be of considerable benefit for patients suffering from cancer-related anaemia. When used in this way it improves red blood cell levels and hence reduces fatigue, one of the most common and debilitating complaints of cancer patients. It all seemed fairly obvious: the literature showed that a low haemoglobin count is associated with poor outcomes in such patients, and increasing the haemoglobin can significantly improve quality of life. Improving the quality of life generally has some bearing on survival and disease progression in cancer patients, and no-one had any serious worries about this subject.

That was until the publication of two studies that appeared to show that patients taking erythropoiesis-stimulating proteins (ESPs) had worse outcomes in terms of survival. The results were unexpected, not least for the investigators, and prompted many to wonder whether the established view of ESPs was correct.

In 2003, Michael Henke, from the University Hospital, Freiburg, Germany, and colleagues, published a study which showed results that surprised both the authors and fellow oncologists (*Lancet* 2003, 362:1255–60). They ran a multicentre, randomised, placebo-controlled trial in 351 patients with low haemoglobin levels who suffered from head and neck cancer. All the patients given epoetin ß had considerable improvements in their haemoglobin levels compared with those who were on placebo. This was as expected. But what came as a shock to Henke were the findings on disease control and survival – in both cases the outcomes were worse in the ESP group. "Despite a reliable rise in haemoglobin concentrations, we saw no benefit for locoregional progression-free survival, locoregional

Michael Henke: findings were the opposite of what we expected. We are waiting anxiously for our next results

progression, or survival," said the authors. "On the contrary, patients given placebo fared significantly better than those given epoetin ß. A contribution of study design to this unexpected finding is unlikely."

Surprise results

"We knew that patients who had hypoxia didn't react as well to radiotherapy as those who didn't," says Henke. "There is pre-clinical evidence that epoetin increases the radiosensitivity of tumours, and we thought it would therefore improve the efficacy of radiation and chemotherapy. We therefore believed that patients with anaemia undergoing radiotherapy would benefit from having their haemoglobin levels boosted with epoetin. So we were expecting just the opposite results from those we found, which really surprised and disappointed us."

Imbalances with certain subgroups in the trial might have contributed to the negative effect of the drug on outcomes, says the paper, but underlying biological phenomena are also a possibility. Further trials are needed, says Henke, to try and explain the biological mechanism that might underpin the findings, and he is currently looking further into the possibility that tumour cells in some kinds of cancers may express erythropoietin receptors and that they use the erythropoietin system for growth and angiogenesis. If this is the case, he says, the finding could have considerable clinical benefit. "You could look for ways of blocking epoetin expression in the cells and thereby improve results, as well as giving doctors a new way of predicting outcomes more accurately."

Henke's study has, perhaps predictably, come under considerable fire regarding its design, results, and interpretation. He takes a sanguine

Heinz Ludwig: ESP treatment should depend on severity of symptoms. In some subgroups it should be used with caution

view. "When you do research and make an unexpected observation you expect to get criticism. However, I would say to critics that there is no good clinical study that shows that what we have found is wrong. Most previous ESP studies have focussed on quality of life in palliative treatment. We wanted to see if it would heal rather than ameliorate. Another difference is that ESPs have previously been studied mainly in patients with disseminated disease, who would probably have died anyway, whereas we were looking at people with localised cancers in the hope that we could make them well. As far as we are aware, ours is the only properly designed study to look at these issues. We are waiting anxiously for our next results."

The study supports findings from another study of epoetin use (epoetin α) in breast cancer (Leyland-Jones, *Lancet Oncology* 2003 4:459–460). In this trial, the treatment group was observed to have an increased incidence of disease progression compared with the placebo group, and the outcome was higher mortality in the treatment group.

In the light of these studies, last year the US Food and Drug Administration (FDA) convened a panel to scrutinise safety. A spokesman said: "FDA is currently working with sponsors of approved and investigational erythropoietin products to ensure that studies are conducted to investigate possible impact of the drug on tumor growth promotion. Separate from the meeting last May, the product labelling for the erythropoietin products approved in the US (Epogen [epoetin α], Procrit [epoetin α], and Aranesp [darbepoetin α]) have been updated to reflect this new information and revised labelling has been distributed under the cover of Dear Health Care Professional letters to the medical community." The European Medicines Agency (EMEA) currently has no plans to undertake an investigation of its own, and will await the outcome of further studies. So it appears that the jury is still out on this issue.

Amgen, which manufactures Aranesp, said it could not comment on other companies' studies. However, Amgen's European Medical Director, Dietmar Berger, said the company was keeping a close eye on the situation: "Amgen has a robust pharmacovigilance programme that is evaluating the effect of Aranesp on survival and tumour progression in multiple oncology populations with well-designed clinical and epidemiological studies."

He also pointed out that the drug served a real need: "Cancer patients cite anaemia as one of the most debilitating side-effects of chemotherapy. When used in accord with the approved prescribing guidelines, Aranesp effectively corrects anaemia and reduces or eliminates the need for blood transfusions in chemotherapy patients, without the burden of frequent injections and doctor's office visits."

A real need

There is no doubt that anaemia is a problem for cancer patients. Heinz Ludwig, from the Wilhelminenspital, Vienna, Austria, and colleagues from all over Europe, collected data on cancer-related anaemia from 748 cancer

IMAGES OF HOPE

Combatting fatigue can make a huge difference to a patient's quality of life

centres in 24 countries over a six-month period in 2001 (*EJC* 2004, 40:2293–2306). This large study showed clearly that anaemia prevalence and incidence among cancer patients were high, and that anaemia had a strong relationship to poorer outcomes. Treatment for anaemia may not be optimal, say the authors: many anaemic patients, including those with very low haemoglobin levels who fall into the category where they should be treated under existing guidelines, were not treated at all. Of all patients who were ever anaemic, 61.1% did not receive treatment for their anaemia. Most patients who were not treated had haemoglobin levels that were too low, but not disastrously so – 47.2% of those not treated had levels between 10.0 and 11.9 g/dl; but 12.9% who were not treated had levels between 8 and 9.9 g/dl; and 0.9% were below 8 g/dl.

Most patients who began chemotherapy during the study became anaemic. The longer they received chemotherapy, the greater their risk of developing anaemia: it was reported in 19.5% of patients in the first chemotherapy cycle and 46.7% in the fifth cycle. Even in the anaemic group with the highest levels of haemoglobin (10–11.9 g/dl) their anaemia had a significant impact on performance status. Using the physician-reported WHO score, it was shown that performance status worsened as haemoglobin decreased, and the correlation was significant. Over half the patients with severe anaemia (haemoglobin less than 8 g/dl) had poor scores, and even among those with haemoglobin levels of 10–11.9 g/dl, one quarter had poor scores. This association is consistent with findings that show a correlation between increasing haemoglobin and quality of life, the study said.

"From the biological point of view it's

EORTC Guidelines for use of erythropoietic proteins in anaemic patients with cancer

Anaemia is a frequent finding in cancer patients and should be carefully assessed. Additional causes of anaemia such as iron deficiency, bleeding, nutritional defects or haemolysis should be corrected prior to erythropoietic protein therapy. The following recommendations are related to adult cancer patients with solid tumours or haematological malignancies:

- In cancer patients receiving chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90–110 g/l based on anaemia-related symptoms.
- In patients with cancer-related anaemia not undergoing chemotherapy and/or radiotherapy, treatment with erythropoietic proteins should be initiated at a Hb level of 90–110 g/l based on anaemia-related symptoms.
- Erythropoietic proteins may be considered in asymptomatic, anaemic patients with a Hb level of 90–110 g/l to prevent a further decline in Hb, according to individual factors (e.g., type/intensity of chemotherapy, baseline Hb).
- For anaemic patients who are transfusion-dependent, erythropoietic proteins should be initiated in addition to red blood cell transfusions.
- We do not recommend the prophylactic use of erythropoietic proteins to prevent anaemia in patients undergoing chemotherapy and/or radiotherapy who have normal. Hb values at the start of treatment.
- Elderly patients experience the same benefits from treatment with erythropoietic proteins as younger patients.
- The target Hb concentration should be 120–130 g/l.
- The two major goals of erythropoietic protein therapy should be to improve quality of life and prevent transfusions.
- The use of erythropoietic proteins with the aim of improving survival or response to treatment is not recommended as there is no evidence to support this. Further studies are needed.
- Within reasonable limits of body weight, fixed doses of erythropoietic proteins should be used.
- We recommend the dosing of erythropoietic proteins according to Fig. 1. However, the decision to dose-escalate cannot be generally recommended and must be individualised. Treatment should be continued as long as Hb levels remain ≤120–130 g/l and patients show symptomatic improvement. For patients reaching the target Hb, individualised titration of lowest effective maintenance dose should be made repeatedly.
- Despite the common use of epoetin α QW (40,000 IU), there is limited evidence to support this dosing

clear that anaemia in cancer patients should be corrected," says Ludwig, "and the trigger for ESP treatment should be the degree of symptoms. This will vary in different groups. For example, a 75-year-old man with heart disease and mild anaemia would benefit from just a small increase in haemoglobin levels – he would have less angina. But a young person can tolerate a higher degree of anaemia, and I would personally start treatment later. It's important that treatment is individualised within existing guidelines. However, guidelines by their very nature are fairly general – if they are not, they are just too complicated for anyone to follow, and they are bound to end up as a compromise."

As to the effect of ESPs on survival, Ludwig and colleagues did not see a negative impact. However, there may be sub-groups where they should be used with caution, he says. "In patients with solid tumours and high tumour mass or people who were incompletely resected, we should probably be careful about recommending ESPs, but in other groups we should exploit their benefits," he says.

A Cochrane systematic review of the effect of ESPs used to prevent or treat anaemia in cancer patients was updated in May 2004, after the publication of the two studies causing concern (Bohlius et al, The Cochrane Database of Systematic Reviews 2004, 3: CD003407.pub2). The authors found consistent evidence that ESP administration reduces the risk for blood transfusions, and that for patients with haemoglobin levels below 10 g/dl

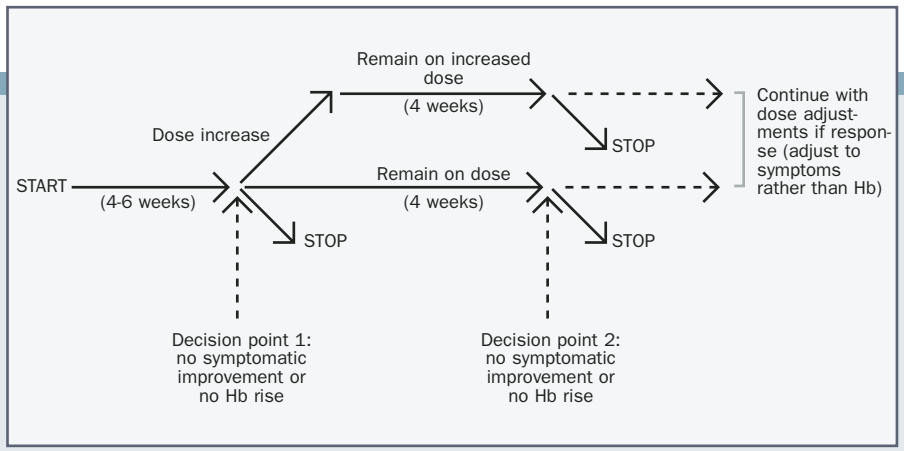

Fig. 1 - Suggested dosing algorithm for erythropoietic proteins in patients with cancer. The target haemoglobin (Hb) levels are discussed in the box and are not above 130 g/l

schedule. The QW application of epoetin ß (30,000 IU) has been shown to be effective in patients with non-myeloid haematological malignancies. The QW administration of darbepoetin α (2.25 µg/kg) can be recommended. There is currently limited evidence to support the use of darbepoetin α in Q2W, Q3W or Q4W dosing intervals.

■ The use of higher initial doses of erythropoietic proteins can currently not be recommended as a standard approach with epoetin α or epoetin ß, but limited evidence exists for darbepoetin α. Further studies are needed.

■ There are no predictive factors of response to erythropoietic proteins that can be routinely used in clinical practice; a low serum erythropoietin level (in particular in haematological malignancies) is the only verified predictive factor of some importance. Values must be interpreted relative to the degree of anaemia present.

■ For patients undergoing autologous blood stem cell transplants, the effects of erythropoietic proteins have not yet been convincingly shown and they cannot therefore be recommended.

■ For patients undergoing allogeneic blood stem cell transplants, the clinical impact of erythropoietic proteins is limited and they can only be recommended on an individual basis.

■ The fear of pure red cell aplasia should not lead to erythropoietic proteins being withheld in patients with cancer.

■ When using erythropoietic proteins to treat anaemia in cancer patients, the combined analysis of all study data indicates a slightly increased risk of thromboembolic events. However, this may be related to the target Hb level achieved.

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it improved haematological response. However, they conclude: "There is inconclusive evidence whether erythropoietin improves tumour response and overall survival. Research on side-effects is inconclusive."

Jan Foubert, President of the European Oncology Nursing Society, who runs a specialist fatigue clinic at the Institut Bordet in Brussels, Belgium, says that ESPs are helpful in boosting energy levels and controlling fatigue in the patients he sees. "In studies of anaemia in cancer patients, we see improvement in the haemoglobin levels when they take ESPs." He adds, however, that there is a need for more research into the link between fatigue and anaemia especially in elderly cancer survivors. Research is also needed into the link between fatigue and depression, anxiety and sleep disturbance, and into how activity may help in managing fatigue.

Foubert worries that the results of the Henke and Leyland-Jones studies may hinder attempts to get the problem of anaemia in cancer patients taken more seriously and dealt with more consistently. "The significance of anaemia and fatigue to the patient is

Jan Foubert: Anaemia-related fatigue is a heavy burden for cancer patients. We shouldn't jump to conclusions

Giovanni Apolone: Existing guidelines are sound. More research is needed to explain the unexpected results

often overlooked in routine assessments, and optimal methods for assessing and treating these conditions remain unclear," he said. He is confident that treating anaemic patients with ESP helps their quality of life, and feels that there were probably problems in the design of the studies that showed worse outcomes. "We shouldn't jump to conclusions. New guidelines are very careful about the target level, the duration and follow-up of treatment, and the endpoints."

Falling prices

One of the reasons why ESPs are not used more widely to treat anaemia in cancer patients is cost. In Italy, for example, the national health service will reimburse ESP treatment for only a small and limited group of patients – anaemic patients with chronic renal failure undergoing dialysis, and cancer patients suffering chemotherapy-associated anaemia. Yet in 2001 ESPs ranked fifth in terms of total out-of-hospital expenditure on drugs by the Italian national health service, accounting for 209 million euros, or 1.7% of total drug expenditure.

The high prices make ESPs a major earner for the industry; according to the *IMS World Review*, they ranked seventh in global sales figures for 2003, coming in at $10.1 billion, after cholesterol and triglyceride reducers, antiulcerants, antidepressants, antirheumatic non-steroidals, antipsychotics and calcium antagonists (plain).

However, this may now be set to change, and Ludwig argues that price cuts and the advent of biosimilar drugs will mean that epoetin will soon become a standard treatment for cancer-related anaemia. The problem is, given the question marks thrown up by the results of recent trials into the impact of ESPs on tumour progression and survival, which patients stand to benefit and which to lose?

Giovanni Apolone of the Istituto Mario Negri, Milan, Italy, recently wrote an editorial on the subject for the *European Journal of Cancer* (vol 40:1289–1291). He believes existing guidelines issued by regulatory authorities are sound. "Within the indications of the FDA, EMEA and other international and national regulatory agencies, at present ESPs should be considered a class of drugs that has received a quite complete assessment in terms of risk-benefit analysis. Several systematic reviews and meta-analyses support these indications. Basically, although some differences do exist between countries, the use of ESPs in patients with cancer to treat or prevent anaemia secondary to cancer or resulting from its treatment is recommended for treatment in patients with severe anaemia, as an alternative to blood transfusion. In less severe anaemia, the decision to give epoetin should be determined by a careful examination of the clinical circumstances," he says.

To address this situation, EORTC have recently produced a set of guidelines for ESP use in cancer patients (see pp 18, 19).

He adds, however, that the unexpected correlations found between ESPs and worse prognosis in the two studies on head and neck cancer and breast cancer show the need for further research. "We need to carry out more studies in the light of such unexpected results as Henke's. These should either be entirely new or re-evaluations of old studies in order to have a better understanding of the reasons for these results. These could be due to the expression of biological factors regulating or modulating the clinical expression of these drugs, and we need to know if they exist and what they are.

"There is some pre-clinical evidence that some cancers (breast, prostate, and ovarian) possess erythropoietin receptors and that these cells may proliferate in response to epoetin use, but there are other cancers, such as small cell lung cancer, where this phenomenon could not be demonstrated. What is needed is translational research to confirm results from these pre-clinical studies in randomised clinical trials in a homogenous population, and with an accurate and systematic collection of information that allows for stratification of subjects in various categories according to receptor status (presence and quantities)."

Until further trials are done, says Apolone, we cannot know whether the guidelines need to be amended, and he urges the industry to focus on this task. "Pharmaceutical companies marketing variants of epoetins worldwide, instead of arguing about the internal and external validity of available evidence from controlled clinical trials, should facilitate and support new pre-clinical studies to discover the biological basis of the unexpected clinical results." In the meantime, he says, the use of ESPs outside the existing guidelines should be considered only in the context of very well planned and carefully monitored clinical studies that implement strict ethical safeguards for patients.

Brainwaves
in drug delivery

David Brayden*

Delivering drugs through the blood-brain barrier has always confounded scientists, but new developments in both non-invasive targeted brain delivery and brain-implanted drug formulations may provide a way forward.

Getting drug therapies into the brain to treat life-threatening illnesses is one of the most challenging issues in drug delivery. Many drugs display excellent affinity for their targets in cell cultures and isolated preparations, but remain undeveloped because they cannot get access to the brain. Companies working on the central nervous system may be able to translate potent molecules into significant patient advances if they only considered the delivery and targeting issues more carefully.

According to a 2004 study by the Tufts Centre for the Study of Drug Development, central nervous system (CNS) drugs are more costly and take longer to develop than other therapeutic classes, but the rewards extend over a longer period. The study found they take, on average, 115 months to develop, at a cost of US$527 million; lifecycle sales peak at US$849 million, nine years after launch. If delivery issues could be resolved at earlier stages of development, leads might emerge more quickly.

A number of false dawns in the 1990s suggested the blood-brain barrier (BBB) could be breached using either a range of drugs to reversibly loosen the BBB cells or by chemically modifying drugs, making them more likely to permeate it. These approaches failed, however, because of a lack of sustained and adequate delivery and also safety issues. This has led to scepticism about new delivery approaches, even though preclinical research suggests breakthroughs may be possible.

Gene delivery to the brain

At the annual meeting of the Controlled Release Society (CRS) in Hawaii in June 2004, Dr William Pardridge of the University of California highlighted some of the pioneering work of his laboratory – on delivering gene medicine to the brain by targeting receptors on the BBB. Typically, the BBB keeps water-soluble agents out of the brain and favours access for small fat-soluble drugs such as diazepam. Water-soluble molecules such as levodopa and glucose can, however, cross the barrier by being carried on capillary membrane transporters, many of which are still undiscovered.

One problem is usually enough for most scientists, but Pardridge is trying to solve both brain and gene delivery using a single molecular targeting tool[1]. In justifying his methods, he argues that the more conventional approach – using transcranial injections of genes in viral carriers – gives rather weak results in confined brain regions, which is not much use for diseases that spread throughout the brain such as Alzheimer's and some advanced cancers. In addition, there are concerns about the inflammatory and autoimmune side-effects associated with the viral carrier itself.

What Pardridge is trying to do is administer tiny fatty particles loaded with genes to the blood, which brings the particles to the brain capillaries of the BBB as it circulates around the body (see box on page 24). The particles are specifically targeted to capillary endothelial cell receptors to which antibodies on the particle surface can bind. Once across the barrier, the gene is then free to disseminate within the brain and be expressed in all or selected regions. This approach is non-invasive and would not require surgery.

These particular receptor targets were chosen as a result of promising rodent data. Somewhat unexpectedly,

DELIVERING GENES VIA LIPOSOMES

The University of California's laboratory work on delivering gene medicine to the brain uses particles long-established in drug delivery products, fatty globules (liposomes). The liposome construction comprises 85-nm-diameter multi-lamellar anionic units coated with polyethylene glycol (PEG) polymer. It is, in other words, a negatively charged non-sticky onion-like system. PEG was used in order to avoid recognition and removal of immunoliposomes by macrophages; hence it improves particle stability and circulation time. A small proportion of the PEG is then attached to monoclonal antibodies designed to target endothelial cell peptide receptors for either transferrin or insulin. Plasmid DNA containing the gene was entrapped in the liposomes and the exteriorised material chemically removed.

the particles had traversed the barrier and entered brain neurons. Data presented at the meeting showed widespread delivery of gene markers throughout the brains of rodents and monkeys using loaded particles targeting the transferrin and insulin receptors respectively. In one pre-clinical example, intravenous injections of particles containing genes for a deficient enzyme improved motor function in a rat model of Parkinsonism[2].

A second example demonstrated a 100% increase in survival time in mice implanted with an experimental human brain cancer following weekly injections of an agent to silence gene expression of a cancer-associated growth factor[3]. Specific growth factors encourage cell proliferation and their receptors tend to be expressed in many cancers in an unregulated way. These data from Pardridge suggest his approach to silencing genes coding for cancer-implicated receptors may be appropriate to take into humans. They showed a 90% reduction in gene expression for the suspect receptor.

A PARCEL WITH TWO ADDRESSES

Pardridge's particle system is a complex formulation and one of the first to demonstrate targeting from two antibodies on the same particle. It has been described as a parcel with both a primary delivery address (to the BBB) and a secondary forwarding address (to the brain cancer). The particle therefore acts as a Trojan horse, and the cargo is released only when the particle enters the cancer and is activated by a tissue-specific trigger.

Pardridge told the conference that this was one of the first drug delivery technologies to prolong life in animals and that it should soon be ready for clinical trials to deliver nerve growth factors (neurotrophins) for stroke. Outcomes in man are unknown, however, and could fail for many reasons. One issue is whether humans have sufficient BBB receptors to transport enough particles. Another is whether there will be sufficient drug or gene delivery from each injection to treat chronic brain disease. Despite these unknowns, the technology has come a long way. Many doubted whether such a complex tri-partite system could work even in animal models.

Dr Jorg Kreuter of the University of Frankfurt, Germany, also provided convincing pre-clinical data at the CRS conference that supports the thesis that drug-loaded particles can be delivered to the brain. His somewhat larger particles were made from a glue-like polymer, and coated with a detergent (polysorbate 80). Kreuter believes the detergent coating attracts lipid carrier proteins in the blood, and then binds to cholesterol-related (low density lipoprotein) receptors on the BBB, leading to particle uptake by the brain. He also suggests the particles could open the tight junctions between the cells of the BBB capillaries, further aiding absorption to the brain. They also block the BBB efflux transporters on the capillaries that normally act in a protective fashion to send toxins back from the brain to the blood. By the same token, efflux transporters also prevent the delivery of clinically useful agents to the brain.

Irrespective of the mechanism, however, data showed that poorly-delivered agents such as the anticancer, doxorubicin, could be made more effective against solid cancers in rats when these particles were used. A second example was the induction of pain relief in rats using an opiate as the cargo. There seems little doubt that the capacity of particles to deliver drugs and genes to the brain has been underestimated.

ANY ADVANCE ON WAFERS?

An alternative approach to getting drugs to the brain has been to bypass

The particle acts as a Trojan horse, releasing its cargo only when it enters the cancer

Drugs discarded due to poor pharmacokinetics could be retried using the new delivery systems

the BBB altogether and implant localised controlled release formulations directly into areas of brain lesions. This is an invasive approach that has had relative success in man. In 1996, Guilford Pharmaceuticals' Gliadel 'Wafer' was approved by the FDA as a treatment for recurrent high grade malignant brain glioma, a condition in which patients typically succumb within 12 months. Seven or eight dime-sized wafers are implanted into the cavity left by the surgical removal of the recurrent glioma. The wafers are made of a biodegradable polyanhydride polymer and contain the anticancer, carmustine, which is released in the cavity as the polymer dissolves.

In theory, the controlled release of the agent should kill any cancer cells not removed by surgery. Controlled release of localised carmustine also suggests the drug's side-effects may be less than when administered intravenously. A major issue with these types of formulations, however, is how to prevent dose dumping in the brain. In a recent clinical trial of Gliadel, the median survival in selected patients with severe types of glioma was reported to have increased by 41% from 20 to 28 weeks. An eight-week extension of life is regarded as significant for this kind of malignant brain cancer, which has few treatment options. Importantly, Gliadel has recently gained a wider indication from the FDA and wafers can now be inserted at the time of the initial surgery and diagnosis. In combination with surgery and subsequent radiation, this change in labelling has expanded the Gliadel market. In 2003, annual sales were US$20 million at an average cost of US$10,000 per patient, a 32% increase over 2002.

Another paper presented at the conference, by Dr Jon Weingart of Johns Hopkins University in the US, described recent studies to further develop wafer technology for other cargos and to tailor the device to release drug cocktails in a programmed manner. Positive pre-clinical studies were described in which two other anticancer agents (paclitaxel and camptothecan) were formulated into biodegradable polymers and used to treat rodents with glioma implants. Other wafer formulations include anti-angiogenesis agents, cancer vaccines and gene-silencing agents.

There is also significant potential to combine intracranial implantation of chemo-therapeutics with the systemic delivery of a secondary agent to achieve additional benefit. One example is the use of a wafer-laden antibiotic (minocyclin) in combination with intravenous carmustine to treat glioma in rats[4]. This technology extends the design kinetics of how cargos are released. By using implanted biodegradable scaffolds, anti-cancer agents that would normally only be able to reach the required sites in cytotoxic levels, can be delivered directly to experimental CNS models of solid tumours. The university-based group are also working with Guilford Pharmaceuticals to screen new classes of more stable and potent anti-cancer agents for their suitability for local brain glioma therapy in future clinical trials.

While wafer implant technology is promising and appropriate for life-threatening malignant localised gliomas, the potential for non-invasive particle-based delivery systems cannot be overlooked. These particles have shown they can access receptors expressed on the blood-brain barrier and deliver cargo to animals. Intravenously-administered targeted particles carrying genes and drugs that can access lesions in the brain would represent a significant breakthrough in the way a range of CNS diseases is treated. These delivery systems could be used to re-examine drugs that have been discarded because of their poor pharmacokinetics and also to optimise the delivery of new candidates. The question now is whether these new particle systems can work as well in human trials as they have done in animals.

*Dr David Brayden is chairman of the UK-Ireland chapter of the Controlled Release Society and a principal investigator at the Conway Institute of Biomedical and Biomolecular Research at University College, Dublin, Ireland.

References
1. *Nature Reviews* (2002) 1:131-139
2. Zhang et al. (2004) *Human Gene Therapy* 15:339-350
3. Zhang et al. (2004) *Clinical Cancer Research* 10:3667-3677
4. *J Neurooncology* (2003) 64:203-209

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Jean-Claude Horiot: the innocent inquisitor

➜ Interview by Anna Wagstaff

In 1972 Jean-Claude Horiot left a wonderful research job in the US to join a cancer centre in Dijon that was too small to conduct clinical trials on its own. He teamed up with similar centres, and in so doing laid the basis for cooperative research and helped end a culture in which medics and hospitals answered to no-one for the quality of their work.

You led the development of international cooperative clinical research, which groups like the EORTC have used to great effect in the past 25 years. What prompted you to undertake this mammoth task?

JEAN-CLAUDE HORIOT When I graduated as a radiation oncologist in the late 1960s, only a handful of very large institutions, such as the cancer institutes in Amsterdam or in Villejuif, were carrying out clinical research. They were very elitist, and having done my medical training here in Dijon, I knew I had no chance of going into research in Europe.

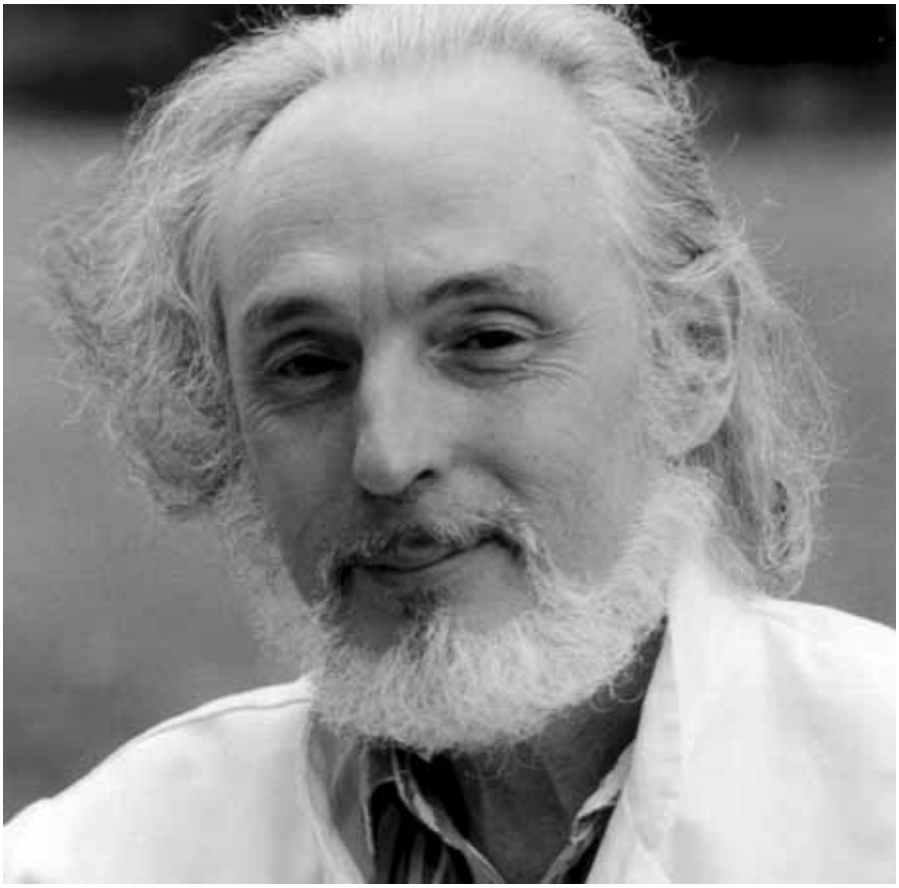
So I decided to build my career in the US. After gaining the US-equivalent qualifications, from MD upwards, I joined the MD Anderson hospital in Houston, and had a wonderful time doing clinical research, where basic, translational and clinical research were all carried out under one roof. But then an academic position opened up in my own city, Dijon, and I decided I would challenge the only candidate – who was from Paris. And to my great surprise, I was nominated.

In 1972 I found myself back in Dijon with an academic position and the remit I had always wanted – to develop research. But I was in a medium-sized centre that was not nearly big enough to carry out clinical research of any weight – at least not on its own.

I was convinced that cooperation between hospitals of this sort of size was the only way to get the necessary critical mass to carry out meaningful clinical research.

This is when I came across the European Organisation for Research and Treatment of Cancer [EORTC], which was exactly what I needed to accomplish what I wanted to do.

The great encounter I made there was with another man of my age, Emmanuel van der Schueren – 'Manu' – who went on to become one of the great builders of European oncology, not only creating the European Society for Therapeutic Radiology and Oncology [ESTRO], but also promoting cooperation between different oncology disciplines, for instance through the establishment of the Federation of European Cancer Societies [FECS]. He was Belgian and



They said we had helped them convince their directors to invest in more staff or better equipment

had trained in Leuven, but had spent some years at Stanford University, California, MD Anderson's great rival in radiation oncology.
We became great friends, and much of what I contributed to building European cooperative research, was done hand in hand with him.

European cooperation is dreamed of more often than achieved. How did you set about realising your goal?
JEAN-CLAUDE HORIOT The first step was to create a radiotherapy group within EORTC, which we did in 1974. Until then, radiotherapy had only existed as a subgroup of the radio-chemotherapy group, which was mostly involved in Hodgkin disease.
After this, we rather innocently invented the concept of 'quality assurance' in research trials. We wanted to include centres in many different countries in a single protocol, so we had to find a way to check that the data gathered in each centre was accurate and reproducible. We had to be certain, for instance, that 1 rad (the unit of radiation dose in those days) in Amsterdam was the same as 1 rad in Leuven, Dijon, Milan, Gothenburg and Lisbon. I visited all the partici-

Quality assurance has greatly reduced late tissue radiation injuries and accidents

pating centres as part of a team of physicists and clinicians, and we measured the beam qualities and equipment parameters. We checked the methodologies as well as the quality of the equipment, because there was a lot of scope for variation, resulting in inconsistencies.

This was the first time a peer review system had ever been used to evaluate practice as opposed to academic papers. Doctors believed what they did was an art, and could never be checked by anyone else. We were warned that we would be seen as an inquisition and that no institution would give access to a team of 'self-promoted inspectors'. Fortunately, these predictions turned out not to be true. One reason may be that we never claimed our measurements were right and others were wrong. We just wanted to ensure that the data we were pooling from many centres were consistent.

We banished the word 'error' from our language, using previously defined consensual parameters to define variations in measurements as minimal, minor or major. Centres with major deviations had to stop patient entry until they regained compliance. Sometimes it was a problem of human competence and sometimes their equipment was not good enough. Many centres told us later that we had helped them convince their hospital directors to invest in more staff or better equipment, as they were able to say: "Look you have refused us for years, and now we are not good enough to participate in European cooperative trials."

It took just two years to eradicate major deviations and demonstrate that we could all speak the same language. From the first published reports on quality assurance, the process was totally legitimised and established. These principles, which were first developed for research, are now used routinely in radiotherapy units throughout the world.

Did this process apply to radiotherapy alone?

JEAN-CLAUDE HORIOT Once the methodology was proven, everyone recognised the benefits of external independent review, and wanted to participate. Shortly after we had proved the concept, Manu and I were asked to chair the first EORTC Quality Assurance Committee, with the task of developing similar procedures in other disciplines, working with surgeons and medical oncologists to analyse the sequences and parameters in a given procedure or treatment. The process was completed by the mid-1990s and quality assurance is now applied in all areas of oncology research and clinical practice.

You can see the beneficial effects. With better radiotherapy resulting from quality assurance, the incidence and severity of late tissue radiation injuries have considerably decreased, and accidents such as transverse myelitis have been almost eradicated.

Was the quality assurance system enough to allow you to run trials on the scale you were looking for?

JEAN-CLAUDE HORIOT It was a learning process. Our intention had been to use the EORTC radiotherapy group to promote radiotherapy research,

Research takes time and it is vital to make sure that you are asking the right questions

Manu (Emmanuel) van der Schueren, a founding father of ESTRO and FECS, who died of cancer at the age of 56. He shared Horiot's experience of research in the US, and the two of them worked together to build the foundations of European collaborative research

slowed down for several years in cervix, prostatic and rectal cancers. Even though the organ groups were not necessarily doing radiotherapy research themselves, they still didn't want anyone else to initiate trials outside of their group and their conditions. They were trying to assert some kind of 'ownership' over these types of cancer.

By the mid-1980s, we'd proved that we could do our own trials and get internationally recognised results. It became clear that working with joint protocols was in everybody's interests, and this is how we have been working for the last 15–20 years, with remarkable outcomes in head and neck, breast, prostate, rectum and brain tumours. We have learnt so much about the importance of cooperation. Today we have no problems even with trials involving multiple modes of treatment, such as various combinations of radiotherapy and chemotherapy, and possibly surgery and/or an organ-oriented specialty as well.

Another important lesson we learnt, by trial and error, is the importance of high-quality dialogue before deciding on a protocol, because research takes time and it is vital to make sure that you are asking the right questions. We cannot have an indefinite number of really good ideas in a normal life, and we have to select very carefully the topics we want to address in research trials.

Some private doctors may not have mentioned radiotherapy, as they cannot do it at their own clinic

but we soon realised improving technical aspects of radiotherapy was too restrictive and we had to promote pivotal trials for all solid tumours benefiting from radiotherapy. Such research had to be done in very close cooperation with surgeons, medical oncologists and organ specialists.

In the beginning, some of the organ oriented research groups were reluctant to work with us, and tried to deny us the right to initiate trials in 'their' area. For instance, in the mid-1970s and early 1980s, EORTC cooperative research was

When you initiate a trial, it takes anything up to two years to define it, write it, have the concept validated by a peer review process, and then deal with the onerous legal requirements. If it is a large phase III trial, you may need to recruit up to 5000 patients, and this can take another five years. Then it may take an additional three years before you can analyse the results. Which means that once you have asked a question, you will rarely get the answer within eight or ten years. You have to ask the right question, or the answer may

With Sweden's Queen Silvia, then Honorary President of the EORTC. Horiot led the EORTC first as Secretary General and later President between 1994 and 2000

be obsolete by the time you get it, and you will have wasted a tremendous amount of time, energy and money.

For instance, we did a lot of research into optimal fractionation (the number and timing of radiotherapy sessions). Up until the mid-1970s, treatment was given once a day, five days a week, as if someone believed that tumours don't develop on weekends or at night. So we started from biological data, showing that the concept of fractionation should be modified, depending on the speed of proliferation of the tumour and normal tissue, and on the type of tumour and tissues. We showed that treating the patient twice a day was better than once a day, and that using multiple fractions per day made it possible to reduce the overall treatment time significantly. It took 20 years to reach these results.

It was very interesting research, but it was also a very hard lesson, because although these results were very positive – for instance in head and neck cancers we could improve local control by 20% – it never came into standard practice. During the second decade of our trials, similar improvements were achieved by adding chemo- to radiotherapy, and this was a far more practical alternative as it is nearly impossible to treat patients with radiotherapy twice a day – you would need twice the equipment and personnel. So we had spent 20 years demonstrating that the concept was right, but it was barely applicable.

The concept could have been very important. If only we had been able to recruit enough patients to prove the point in five or six years, it would have been very useful in curing a large number of patients and helping to justify the case for strengthening radiotherapy departments.

Would you say that rivalry between surgeons, medical oncologists and radiotherapists is now a thing of the past?

JEAN-CLAUDE HORIOT In cancer institutes, we knew from the early 1970s that what is needed is not a choice between one type of intervention and another, but a multidisciplinary approach. People who work or were trained in cancer institutes cannot imagine working in any other way.

The trouble is that only a minority of patients are treated in cancer hospitals. In France, 80% are treated in general hospitals or private clinics, where the multidisciplinary approach has taken much longer to be established. However, this is changing, and under the National Cancer Plan for 2003–2007, a multidisciplinary approach is mandatory. If a patient is treated outside this system, individual doctors or entire institutions could lose the right to treat cancers.

The National Cancer Plan also gives patients the right to be told about all treatment options. Many patients with prostate cancer, for instance, opt for treatment by radiotherapy rather than surgery. In the past, some private physicians may not have mentioned this option, because they cannot carry out the treatment at their own clinic. But

Europe must hold its own in research or pay commercial prices for every new tool and treatment

There is the ethical price of having the human genome developed and patented purely in the US

the principle of informed consent has now been extended to all cancer patients, so it is much harder for clinicians to get away with this. As patients become better informed, all practitioners know they need to demonstrate that they work to the same high standards as the best cancer institutes or university hospitals.

Are there wide variations in the quality of radiotherapy available within and between the countries of Europe?

JEAN-CLAUDE HORIOT First-class radiation oncology is practised in most European countries, although not every patient in those countries may have access to the best management. The major problem, depending on where you are, is unacceptable delays or limited access to innovative techniques because of staff shortages, outdated equipment, or both.

With the latest techniques, it is not so much the machinery as the software and regular upgrading that is the real expense. Intensity-modulated radiotherapy, for instance, needs a very special multi-leaf collimator (that aligns the particle beam), activated to modify not only the field size but the fluence (rate of particle flow) of radiation to each spot. It is a very sophisticated technique involving enormously complex calculations and equipment monitoring, and you therefore need some extremely powerful software, renewed every year or two years. These techniques also require a huge amount of preparation time from radiation physicists and oncologists, in order to tailor the radiation to each individual patient. So the big difference nowadays is not so much the variation of knowledge as the amount of time one can give to a patient who can benefit from that technique.

The trouble with radiotherapy – and this applies equally to surgery – is that there is no equivalent to the pharmaceutical industry, which can discuss with bodies such as the European Medicines Agency [EMEA] and national health systems to reach agreement to use and fund a novel approach in a rational way. As a result, patient access to innovative radiotherapy can vary a great deal not just from one country to another, but from one institution to another, and even sometimes from one patient to the next within the same institution, which I feel is an ethical problem.

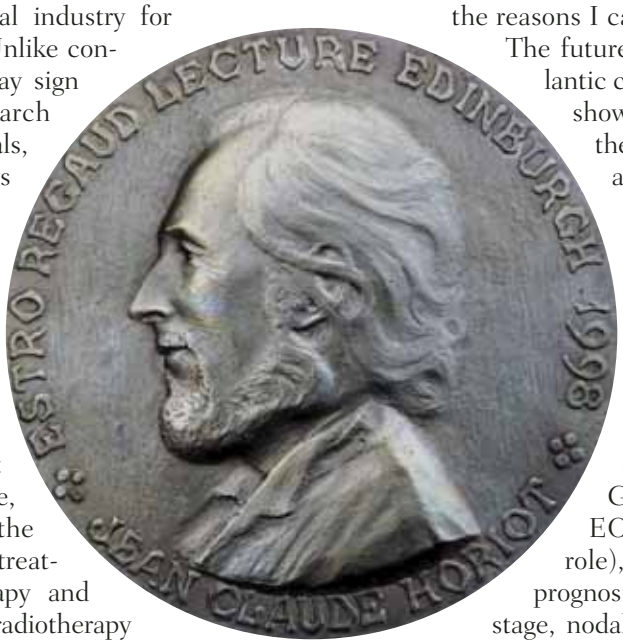
Do you see a time when the countries of Europe will be able to pull together in a coordinated research effort as happens in the US?

JEAN-CLAUDE HORIOT The US benefits from a federal approach. In Europe, under the principle of 'subsidiarity' research is defined as a national goal, and the EC only contributes to what each country cannot organise.

This was the trouble with the Clinical Trials Directive. We had hoped that European legislation on research would help the conduct of international clinical trials, by streamlining legal requirements. As we now know, not only did the Directive endorse the need to spend huge resources satisfying the legislation of each country with a participating centre, but some more European rules were introduced in addition to the national ones. The cost of clinical research has increased to a point where EORTC has to set strict priorities. As a result, some projects originating from EORTC groups have to be developed outside the organisation unless they are top priorities or have adequate funding.

The EORTC, which is by far the largest European group conducting cancer research, gets no support from the EC; it is treated like any other 'expert group' with the right to tender for projects drawn up by the EC. The preparation of an application requires an enormous amount of effort and money and the result is sometimes not

worth the game. We cannot define what we want to do, we cannot choose our partners, and we have to match the funding provided by the EC. In practice, the EORTC has to depend largely on the pharmaceutical industry for most of its funding. Unlike contracts the industry may sign directly with research institutions or hospitals, the EORTC always retains control over how we collect, analyse and publish the data, which is priceless. However, the industry will only fund trials that fit their marketing strategy, which means that if we want, for instance, to research into the difference between treatment with radiotherapy and surgery compared to radiotherapy alone, we have to find funding from other sources, because it is of no interest to the pharmaceutical industry.



Cast in bronze. This medal commemorates Horiot's ESTRO Regaud honorary lecture, delivered in 1998

Many member states hardly invest in clinical cancer research at all, and when they do, the funds tend to go to national projects. This is also true of most cancer charity money. Some research groups are worried about activating European trials in case they jeopardise their chances of getting national funding. This is where the US does so much better than us, and it is very disappointing.

You paint a gloomy picture. Are there any reasons for optimism about European cancer research?

JEAN-CLAUDE HORIOT Europe has to hold its own in research if it is to avoid having to pay commercial prices to access every new tool and treatment. More importantly, there is the ethical price of allowing the techniques, agents and procedures derived from mapping the human genome to be developed and patented purely within the commercial context of US research.

European research has a lot going for it, such as the quality of the relationship between doctors and patients, which is far more constructive and less litigious than in the US, and is one of the reasons I came back.

The future really lies in transatlantic cooperation, which was shown to amazing effect in the Glivec [imatinib] trials in metastatic GIST tumours [gastro-intestinal stromal cell sarcomas], which went from phase I to phase III in less than two years. The current 'planetary trial' TRANSBIG (Breast International Group, in which EORTC plays a major role), comparing classical prognostic indicators, such as stage, nodal status and hormonal receptors with innovative biological parameters, such as genomic profile, is an excellent reason to remain optimistic: 5000 patients to be accrued in 3 years by 39 leading institutions from 21 countries, which stands to benefit a hundred thousand women per year worldwide.

Looking to the future, everything we've learnt about the extraordinary complexity of the regulation of cancer growth makes it increasingly unlikely that a single specific mechanism can result in the discovery of a 'magic pill'. Surgery and radiotherapy will continue to be crucial in early cancer, and the slow but very regular progress we're making in stopping cancer growth for long periods in metastatic patients may revive indications for radiotherapy and/or surgery on these 'sleeping disease spots'. This is a very lively research field and Europe is playing a dynamic role. With a predicted shortage in these two disciplines, my message to all young oncologists is that there are tremendous opportunities to add your talents to the European research effort.

Women doctors offer alternative to costly mammography

Peter McIntyre

Breast examination by specially trained young women doctors is proving effective at picking up tumours in the general population in a number of developing countries. If it can be shown to affect mortality rates, this low-tech screening method could provide a solution for poorer nations, and may even force a rethink in richer ones.

Early detection and quality treatment are twin pillars in the strategy adopted in the West to reduce mortality from a rising incidence of breast cancer. Early detection in this context means mass screening by mammography, backed by better health education about breast self-examination and breast cancer treatment.

But mammography is expensive, difficult to do and detects some cancers that were never going to be a problem. Some argue that other methods of early detection allied to treatment with tamoxifen and adjunctive therapy would save as many lives without detecting so many benign lumps and cancers that would never need treatment. In richer countries with sophisticated healthcare systems doubts tend to be outweighed by the overall success of the strategy. It is assumed that the smaller the lump detected, the better the survival outcome. Consequently, this model has also been proposed as the way forward for other countries considering screening.

Developing countries have neither the resources nor the infrastructure to establish mass screening by mammography, which requires a large number of radiographers to take the films and highly trained radiologists to read them. They have therefore been left with no viable strategy.

The international community consoled itself with the thought that breast cancer is a disease of affluence and of women who postpone childbearing and have fewer children. Increasingly this view is being challenged and the need for early detection in developing countries is being asserted, especially as the lives of women change.

Indraneel Mittra, director general and head of oncology at the Bhopal Memorial Hospital and Research Centre in India, is keen to find alternative routes to screening. He says: "If you ask three different radiologists to read the same mammogram you get three different answers. If you screen 10,000 women for seven years you save four lives. Even in the best countries mammography is hugely complex and to establish this in developing countries is impossible in my view."

In 1997, while working at the Tata Memorial Hospital in Mumbai (Bombay), he set up the first randomised trial of early

Young women doctors explain the breast screening process to women at a Cairo clinic

"Mammography is hugely complex and to establish this in developing countries is impossible in my view"

detection of breast cancer, comparing screening through clinical breast examination with no screening. The trial recruited women from 10 socially disadvantaged areas of Mumbai, dividing each area randomly into a study group and a control group.

Women in the study group and the control group both received health education about breast awareness. In addition, health workers carried out clinical breast examination on women from the study group, referring those with suspicious findings for further specialist examination. In the first batch they enrolled 75,000 women, and another 75,000 in the second batch. In the first round of screening, breast cancer was three times higher in the screening group than in the control group. In the second round the difference was less, but still more than in the control group.

This trial, funded by the US National Cancer Institute and the Tata Memorial Hospital, is now into its fourth round, but Mittra says it is still too soon to determine the outcome. "The objective of screening is not simply detecting cancers early; it is to demonstrate that the screening has been worthwhile. The end point you are seeking is a reduction in mortality."

Mittra believes this trial does demonstrate that screening by clinical examination can be efficiently set up and is acceptable to the population. "It has been a highly complex exercise. You have to screen many women to detect one cancer and you have to pay huge attention to detail."

Egypt was the next country to pilot this model. Vittoria Buffa, wife of the then Italian ambassador to Cairo, wanted to fund an ongoing project from money raised every year at an Embassy bazaar. The fundraising organisers (mainly women) suggested something that would

"Diagnosis of breast cancer is usually late and the prognosis is poor"

promote the interests of Egyptian women. Buffa talked to people at the Italian Hospital in Cairo, who put her in touch with the Challenge Fund, set up ten years ago by the European School of Oncology (ESO) to support health professionals in countries with limited resources.

An international team was formed to oversee the Cairo pilot study, including Salwa Boulos, a radiologist at the Italian Hospital, Mohsen Gadallah, a public health doctor from Ain Shams University Cairo, Alberto Costa of ESO, Indraneel Mittra and Anthony Miller, from the University of Toronto, who worked for 15 years on World Health Organization cancer control programmes, as well as the Canadian National Breast Screening Study. The pilot also won the backing of Egypt's first lady, Suzanne Mubarek.

Anthony Miller: skilled breast examination can find as many poor prognosis cancers as mammography

As a radiologist, Boulos is well aware that breast cancer is not talked about, not diagnosed and therefore not treated in time. "Diagnosis of breast cancer is usually late and the prognosis is poor," she said.

The first phase of the pilot began in May 2000 with about 5,000 women aged 35-64 living in an area around the Italian Hospital. Social workers conducted house to house visits and the 4,116 women who agreed to join were taken through a questionnaire and invited to attend a nearby health centre for examination by young female doctors who had received special training. In all, 2,481 women were examined. Women were given health education messages on the importance of breast care and shown how to do self-examination. Those who had an abnormal finding at clinical examination were referred to the hospital for examination by mammography or for biopsy. They were reassured that whatever treatment they needed would be free.

In this first trawl, 291 women were referred to the Italian Hospital and 20 women were diagnosed with cancer – a rate of eight per 1,000 women who attended for breast examination. This very high rate is not the incidence of cancer, since it included cancers that had developed over a number of years, but it destroys the myth that breast cancer is only a disease of affluent Westernised women. These women from a poor part of Cairo would normally have been considered 'low risk' for breast cancer. Their mean age of marriage was 20.5 years, the mean age of first birth was 21.8 years, 95% had been through one or more pregnancies and 45% had four or more children.

A high number of women – 55 out of 291 referred – did not attend the Italian Hospital despite an abnormal finding. In the second phase strenuous efforts were made to contact these 55 women and encourage them to come forward. Some would not open their doors to social workers. Only 20 were persuaded to attend hospital, and four of these were found to have breast cancer, all with advanced disease.

Gadallah believes that the women who dropped out did not understand the seriousness of the disease or the potential benefits of treatment, or were too frightened. "They knew they had something. The doctor who examined them said there is something wrong with your breast, and you need to go to the Italian hospital to be examined."

Boulos believes there are also a few cases where family pressure was the deciding factor. "We had two cases where the women were under pressure. Both of them died. The first woman's daughter brought her in quite early in the disease. She had been living with her son who had refused to accept the concept of having a sick person in the house. In another case, the

Salwa Boulos: family pressure sometimes prevents women from seeking early treatment

Indraneel Mittra: you have to screen many women to detect one cancer and you have to pay huge attention to detail

woman presented at a very late stage. The husband refused completely to allow his wife to go."

The only deaths known to have occurred in the study have been of women who at first refused to go to the hospital. Nobody knows what the outcome has been for the 35 women who have still not attended.

Phase 2 began in 2001. The original group was randomly divided by area into A and B. Women living in A areas were invited back for a further clinical breast examination and were reminded about how to conduct self-examination. Again those with suspicious findings were referred to the hospital.

In 2003, women in Group B areas were visited by social workers who administered a questionnaire to see whether they had noticed any breast problems. These women were the control group since they were not invited for screening, but any who disclosed a problem to the social worker were invited to the hospital for a mammogram.

The pilot confirmed that young female doctors can detect breast cancers by screening. Miller believes that a study with sufficient power (number of women and length of screening) would show a mortality benefit. "What I think we will find in the end is that the incidence in this

"Her son refused to accept the concept of having a sick person in the house"

relatively young age group is 1.5 to 2 per thousand women, which is still high, but we have recognised that in North Africa there is quite a lot of breast cancer."

The number of women who refused further examination was a concern. However, there was a greater willingness to take part in Phase 2. Boulos said: "The word spread about what we were doing and women had a greater confidence." Gadallah intends to explore the reasons for women refusing investigation, to encourage women that hope from treatment should outweigh fear of the disease. The pilot continues in a new area of Cairo with another 5,000 women.

The next step will be taken in the Yemen. Miller is preparing a protocol after discussing the project with key staff at Kuwait University Hospital in Sana. "There are people there who are expert in oncology and interested in breast cancer, so there is a base for capacity building," he said. Young female doctors will be trained in breast examination and radiologists will receive mammography training. He hopes that in the Yemen it will not be necessary to do a 'Phase 1' and they can proceed from the start with a control group and a study group.

Khadija Al Huraibi, a gynaecologist at the Kuwait University Hospital, is anxious to start as soon as possible. "We met the social workers and the young doctors. The social workers already have experience in going door to door. Our community is a little bit different from Egypt. Women visit each other and are often grouped together in the day. We have the chance to meet 50 women together."

Sudan also wants to test this method of screening. Ibrahim Elfadil, from the National Institute of Oncology in Khartoum, said that breast cancer accounts for 75% of cancers reported in women and survival rates are poor because of late diagnosis.

There is only one specialist centre in the country. He said that the point of doing a pilot would be to establish that an early detection programme was feasible and socially acceptable.

Cultural factors in each country must be addressed for screening to work, to ensure that women attend for examination and for follow-up care. Ethical questions also have to be addressed. If clinical breast examination is known to be effective, is it ethical to conduct a trial where half the population in the study does not receive it? However, effectiveness has not yet been demonstrated in a low-income country. Moreover, the control group receives education about breast care and self-examination so that these women are better placed to detect cancer early than women in the general population.

It is essential that treatment is available and accessible when cancers are discovered, which means that it must be free or heavily subsidised for low-income women. Miller says: "There is no justification in going out to look for cancers and introducing early diagnosis unless we can offer treatment." The pilots include free treatment, but this would clearly become an issue if screening programmes were introduced on a larger scale.

None of these pilots has yet shown the impact on mortality reduction, but it is possible that in a few years' time a meta-analysis embracing India, Egypt, the Yemen and Sudan could give the answer. If this is an effective method of early detection and it does save lives, it could cause rich and poor countries alike to consider whether mammography is the only route.

Miller is already sceptical of the cost-benefits of mammography. "The costs of training and continually doing the screening, and the cost in terms of women found to be abnormal by mammography but found not to have invasive breast cancer, are all very high. Mammography does not find poor prognosis cancers that cannot be found by breast examination if that examination is good."

"There is no justification in early diagnosis unless we can offer treatment"

Poorer countries take their place at the World Cancer Conference

Jose Julio Divino

Last November 800 people working to control cancer in 82 countries across the world gathered in Dublin to share their experiences of what works and what doesn't. This was the fourth World Conference of Cancer Organisations, but for a number of developing nations it was a first.

The World Conference for Cancer Organisations (WCCO) is an initiative of the International Union Against Cancer (UICC), the only international non-governmental organisation dedicated exclusively to the global control of cancer. The Conference seeks to bring together all organisations involved in the global fight against cancer, from small societies with limited funds and reliant on volunteers, to high-profile charity organisations, which raise and dispense large sums of money and employ skilled medical, scientific, educational and administrative personnel.

The 4th WCCO was hosted by the Irish Cancer Society at the end of last year. It was remarkable particularly for the significant attendance from mid- and low-income countries, including Jordan, Libya, Tunisia, Malaysia, India, Ghana, Nigeria, Zimbabwe, Jamaica and Cuba. Also new was a welcome focus on patient advocacy initiatives, such as patient forums, which have provided effective platforms for patients, caregivers and the growing number of cancer survivors worldwide to voice their special needs and concerns to representatives from the medical community and government.

John Seffrin, UICC President and CEO of the American Cancer Society, opened the conference with a rallying cry, calling on delegates to help put cancer on the global political agenda as a higher priority than ever before. "Seven million people will die of cancer this year alone. The untold story is that most of those deaths will be needless. We need to share best practices and knowledge … to work together to develop effective national cancer strategies that make the transition from what is to what could be," he said.

Isabel Mortara, Executive Director of the UICC, highlighted the potential for improvements among the lower-income countries, which bear the lion's share of the world's cancer burden yet suffer a chronic lack of resources in critical areas like screening, public health education and access to treatment and palliative care. "With more effective sharing of knowledge and a more coordinated approach to cancer control," she argued, "developing countries could make great strides forward, even within the context of severe resource constraints."

The proven success of patient advocacy in a number of countries was also seen as a model for progress: "Patient forums and other similar

Ranjit Kaur (right), President of Malaysia's Reach to Recovery Breast Cancer Support Network, with the UICC's Isabel Mortara. Kaur is holding the 2004 Outstanding UICC Volunteer Award for her pioneering work in patient advocacy

groups are already helping change the way health services are delivered in developed countries like the US, UK, Australia and Canada. Our challenge now is to capitalise on this momentum in mid- and low-income nations, where patients often face very tough social, economic and cultural issues," said Mortara.

Ireland proved a timely choice of venue for the event, as it is the first country in the world to implement a total workplace ban on smoking. The ban, which came into effect on 29 March 2004, covers not only shops, factories and offices, but also restaurants, pubs, clubs and bars. In his welcome address to delegates, Irish Prime Minister Bertie Ahern applauded his country's "landmark effort to protect employees, children and others from the toxic effects of tobacco," and urged delegates to take some time out from the very full programme of plenary sessions, symposia and workshops to sample the delights of smoke-free Irish pubs.

The conference programme was tailored to meet the needs of a broad cross-section of the cancer community, including researchers, educators, scientists, health professionals, advocates, programme coordinators, and information and communications officers from public health organisations, patient groups, and governmental agencies. Among the very many topics covered in depth in a packed three-day agenda were: efforts to cut tobacco use, patient advocacy initiatives, national cancer control planning, early detection and prevention strategies, psychosocial factors in cancer care, survivorship issues, and effective marketing and fundraising strategies. Special Spanish- and French-speaking workshops were also held.

The conference saluted extraordinary contributions to the global effort to control cancer at a Gala Dinner held at Trinity College. Four people active in different fields across the globe were presented with UICC awards for their exceptional work. Ranjit Kaur, President of Malaysia's Reach to Recovery breast cancer support network, was recognised for her pioneering work in patient advocacy. Leslie Sobin, chief of gastrointestinal pathology at the Armed Forces Institute of Pathology in Washington, DC, was awarded for his work on the TNM classification of tumours. Awards were also presented to the Finnish Cancer Society, for the effectiveness of its comprehensive tobacco control policies and cervical cancer screening programme, and Micheál Martin, former Irish Minister of Health and Children, for his efforts to implement Europe's first total workplace smoking ban.

Addressing the closing session of the event, Irish Cancer Society Chief Executive John McCormack urged the global cancer community to work together more closely and to use events like WCCO to forge and strengthen international partnerships and networks that will help speed advances in prevention, early diagnosis, treatment and patient care.

Has tamoxifen had its day?

Joanna Lyall

Anastrozole is being hailed by some as the new tamoxifen. But many researchers feel there is a great deal more we need to know before we consider casting aside the hormonal treatment that has served so many women so well.

Trialists of the aromatase inhibitor anastrozole are calling for the drug to replace tamoxifen as the preferred initial treatment for postmenopausal women with localised hormone-receptor-positive breast cancer. A five-year course of tamoxifen is the current standard treatment for this group of patients, which is prescribed to an estimated 500,000 women worldwide. The results of the ATAC trial (Arimidex, Tamoxifen, Alone or in Combination), published in the *Lancet* (365:60–62), showed women treated with anastrozole did better than those on tamoxifen in terms of disease-free survival, time to recurrence, distant metastases, and contralateral breast cancer.

The ATAC study is a double-blind randomised trial, comparing five years of anastrozole alone with tamoxifen alone, or in combination, as adjuvant therapy in 9366 postmenopausal women with localised breast cancer. The combination arm was closed early due to lack of efficacy, so the five-year results compare anastrozole alone against tamoxifen alone. After a median follow-up of 68 months, figures for disease-free survival showed 575 events for women treated with anastrozole compared with 651 for women on tamoxifen (hazard ratio 0.87, 95% CI 0.78–0.97, p=0.01). Time to recurrence was also better for the anastrozole group (402 vs 498, 0.79, 0.70–0.90, p=0.0005). If one looks only at the figures for women with hormone-receptor-positive breast cancer, the benefits are marginally greater: 0.83, 0.73–0.94, p=0.005, for disease-free survival and 0.74, 0.64–0.87, p=0.0002 for time to recurrence. The anastrozole group also did better in terms of reductions in contralateral breast cancers (all patients 35 vs 59, 42% reduction, 95% CI 12–62, p=0.01; hormone-receptor-positive patients 53%, 25–71, p=0.001).

Anthony Howell: anastrozole should replace tamoxifen as first-line treatment after surgery in hormone-receptive breast cancer

Anthony Howell, of the department of medical oncology at Christie Hospital, Manchester, who chaired the trial steering group, believes that these results indicate that anastrozole should replace tamoxifen as the standard treatment in hormone-receptive breast cancer. "On the basis of the ATAC data, we feel it is appropriate to begin adjuvant therapy with anastrozole as first-line treatment after surgery for breast cancer in patients with hormone-receptor-positive tumours," he said. "The reason is that if you start someone on tamoxifen during the first 2.5 years there are quite a lot of relapses which are prevented by anastrozole. When a patient gets a relapse, that usually ends in further systemic disease and,

Henning Mouridsen: tamoxifen is treatment of choice for first two years, unless there are thromboembolic concerns

Andrea Decensi is testing a combination similar to the ATAC combined arm, but with a lower dose of tamoxifen

I am afraid, death. Thus, preventing lapses at all costs is very important."

Overall survival

The study has not, so far, shown any difference in overall survival (hazard ratio 0.97, 95% CI 0.85–1.12, p=0.7). However, the trial group argues that this is to be expected since the trial population had relatively good prognoses: 61% of patients were lymph node negative and 64% had tumours of 2 cm or smaller. They point out that trials of tamoxifen versus placebo took at least seven years to show a significant survival advantage, and argue that the reductions in recurrence and distant recurrence associated with anastrozole strongly suggest that a reduction in deaths from breast cancer will eventually be seen.

"We are already seeing fewer metastases and this trend is going to get stronger," said Howell.

But other researchers believe the results of the study do not provide sufficient evidence to warrant abandoning tamoxifen as the first-line treatment for this group of women. Their reservations concern the lack of evidence about the long-term effects of anastrozole, and the fact that we have no way of predicting which women are likely to benefit from it. There are also concerns about the cost and questions about length of treatment.

Henning Mouridsen, professor of oncology at Rigshopitalet, Copenhagen, has recently reviewed the role of aromatase inhibitors in the treatment of postmenopausal women with early breast cancer (*EJC*, in press). He considers that while aromatase inhibitors have an important role in adjuvant treatment, their long-term superiority over tamoxifen remains uncertain. He believes that the optimal treatment approach still needs to be defined, and argues that sequencing tamoxifen with an aromatase inhibitor may prove superior to non-sequenced therapy with an aromatase inhibitor.

Mouridsen's view is that tamoxifen should remain the treatment of choice for the first two years, with a possible switch to an aromatase inhibitor at that point. "The key scientific question yet to be answered in randomised trials is whether any superiority is associated with the upfront or the sequential approach," he said.

He points out that at the international conference on primary therapy of early breast cancer in St Gallen, Switzerland, in January, the consensus panel was in favour of maintaining tamoxifen as the standard treatment for postmenopausal women with early breast cancer.

"Tamoxifen is still the treatment of choice for the first two years unless there are thromboembolic concerns," he said.

Andrea Decensi, director of the chemopreventive division of the European Institute of Oncology, Milan, and director of the division of medical and preventive oncology at Galliera Hospital, Genoa, believes the increased risk of endometrial cancer associated with tamoxifen could be addressed by reducing the standard dose. Preliminary results of a cooperative Italian Norwegian study headed by Decensi show that reducing the amount of tamoxifen by three quarters is still effective in reducing the incidence of breast cancer.

He believes the best answer may lie in combining tamoxifen with anastrozole, and says that the problems with the combination arm of the ATAC trial might have been due to the dosage: "I

"Fewer recurrences and metastases suggest anastrozole may eventually show better survival"

"Tamoxifen may still be effective when used at one-quarter of the standard dose"

think 20 mg per day of tamoxifen might have been too high in combination with anastrozole." He is currently studying the effects of a combined Arimidex and tamoxifen regimen using a lower dose of tamoxifen.

Martine Piccart, head of medical oncology at the Jules Bordet Institute, Brussels, is coordinator of the TRANSBIG trial into genetic targeting of breast cancer treatment. She believes the problem lies less in the choice of drug than the choice of patient. "We are entering an era of individualised treatment and at the same time we are lacking strong predictive tools for judging which women will do best on which treatments," she said.

She is not convinced that five years of endocrine therapy is enough for women at high risk. "We have five very positive trials and my personal view is that most women who I see in my clinic should be considered candidates for an aromatase inhibitor. But that is not to say that all women should be given anastrozole from the beginning and for five years. Things are more complex than that. The ATAC trial is certainly the longest follow-up but the benefits are still relatively small in percentage terms.

"We now have two trials showing that two years of tamoxifen and then an aromatase inhibitor is effective. I am very tempted to go for tamoxifen and then an aromatase inhibitor in women whose tumours express high levels of estrogen and progesterone receptors."

Side effects

The ATAC trial found that, compared with tamoxifen, treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding, hot flushes and vaginal discharges. However, there were more fractures and more arthralgia among women on anastrozole than among the group on tamoxifen.

Fracture rates per 1,000 woman years were 22.6 for anastrozole and 15.6 for tamoxifen. The risk ratios for all the prespecified adverse events were similar, says the trial group, to results in two analyses conducted earlier in the trial (*Lancet* 2002, 359:2131–39; *Cancer* 2003, 98:1802–10), suggesting that that the safety profile of anastrozole remains unchanged during the five-year treatment period. "No new safety concerns emerged," they said.

Howell points particularly to the drop in the incidence of endometrial cancer, from 0.8% of women on tamoxifen to 0.2% of women on anastrozole. This, he argues, has a wider significance on women's quality of life because of the spin-off effect on cutting down the number of hysterectomies – many of which may be unnecessary. "Gynaecologists are rightly worried that any form of prob-

Martine Piccart: we need ways to predict who will respond best to which drug, used alone, in sequence or in combination

lem in the uterus may lead to endometrial cancer on tamoxifen and I suspect this leads to the excess of hysterectomies." he said. The results show 5.1% of women on tamoxifen had hysterectomies compared to 1.3% of women on anastrozole." The problem of increased fractures, he argues, can be managed by bisphosphonates.

The ATAC group also point out that withdrawals due to drug-related serious adverse events were significantly less common with anastrozole (4.7% vs 9.0%). "Since almost all patients have completed their scheduled five years of therapy, the safety and tolerability of therapy can be deemed final," the study concluded.

Class effect?

The ATAC study, says Howell, is the largest study ever done in early breast cancer, and its results have been treated as reliable as far as anastrozole are concerned. But how much does it tell us about the effects of aromatase inhibitors as a class of drugs?

The trial group stipulate that the results are only applicable to anastrozole "since it is unknown how differences between the aromatase inhibitors affect their clinical usefulness." However, Howell believes that there may be a class effect, though treatment decisions must be made on the basis of best evidence.

"As a clinician you treat somebody with the drug with which you have most experience. At the moment we have most evidence on anastrozole. But in five years it may be letrozole.

"All the aromatase inhibitors are associated with fewer deep vein thromboses and a good gynaecological profile. They are all associated with osteoporosis and increased joint aches in some women," he said. He added, however, that "exemestane and letrozole are associated with increased cardiac deaths which are not seen on anastrozole."

Mouridsen also feels it is too early to say whether there is a class effect for aromatase inhibitors. He argues that, while there clearly are differences between their mode of action and potency, we lack data that can relate these differences to clinical activity. He believes that while the evidence for aromatase inhibitors grows increasingly strong, many questions remain about the most effective use of tamoxifen and aromatase inhibitors in adjuvant treatment. "These questions relate primarily to the optimal single agent or sequence, duration of treatment and selection of individual patients," he said.

The ATAC trial seems to point to a growing role for aromatase inhibitors in the treatment of postmenopausal women with early breast cancer, in particular in patients at cardiovascular risk.

The trialists argue that the higher rates of recurrence, especially in years 1–3, and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, "lend support to the approach of offering the most effective and tolerated therapy at the earliest opportunity." Many other seasoned researchers, however, urge caution before ditching tamoxifen, which has served hundreds of thousands of women so well over the last three decades.

More time is needed, they argue, to evaluate the impact on survival and the long-term toxicity of anastrozole. And further research is needed to establish whether anastrozole is really more effective when prescribed alone rather than in combination or sequenced with tamoxifen, and to identify which women are most likely to benefit and the optimum length of treatment duration.

"Fears of endometrial cancer on tamoxifen may lead to many unnecessary hysterectomies"

Decensi, who is involved in a separate study on tamoxifen and anastrozole, is concerned about the lack of data on the potential long-term toxicity of anastrozole. "This is a good study and it's clear the new drug has potent advantages. But we have to be very prudent. Toxicity may become apparent after several years," he said. The fact that fractures and arthralgia are higher among women on anastrozole is also a concern for clinical practice, he added.

Decensi also points out that cost is an issue here, as anastrozole is much more expensive than tamoxifen. He believes the new drug can only be justified as a first-line treatment in women who are at cardiovascular risk. Piccart concurs with Decensi that the side-effect benefits of anastrozole over tamoxifen are relatively small in percentage terms.

Look – no strings!

Patient groups are seeking to redefine their relations with the industry

➜ Anna Wagstaff

As patient groups begin to gain access to the corridors of power, the spotlight is falling on their relations with the powerful pharmaceutical industry. In an effort to protect their credibility from a murky sea of rumour and speculation, many patient groups are now trying to negotiate a more transparent and arm's length relationship with their industry sponsors.

A Parliamentary Committee in the UK has been hearing damning allegations about relations between pharmaceutical companies and patient organisations, as part of an investigation into the influence of the industry.

Patient groups have been accused of acting as 'stooges' for the pharmaceutical industry, Trojan horses under whose cover the industry has been able to infiltrate policy-making bodies. Criticisms range from Biogen setting up Action for Access to campaign for reimbursement of one of its multiple sclerosis drugs – it was later shut down by the regulators – to the time when the long-established Alzheimer's Society sent out a statement from a drugs company under its own name. Questions have been asked as to why, in the debate over the safety of selective serotonin uptake inhibitors (SSRIs), one mental health group which has kept a distance from the industry was highly critical, while two others, who take industry sponsorship, were silent. The Association of the British Pharmaceutical Industry came under fire for allegedly describing patient groups as 'ground troops' that they could use to weaken "political, ideological and professional defences" against direct to consumer advertising.

Similar debates are taking place in other countries. The issue has come under the media spotlight in the Netherlands – the only country in Europe to set aside 30 million euros a year for patient groups. It is also a hot topic in Germany, where a number of cancer patient groups have been criticised for taking money from the industry. European umbrella groups, which have mushroomed in order to have an input into the EU consultation processes, have also proved rich targets for rumour and speculation.

Taken together, a few examples of bad practice, a greater number of allegations, and a murky atmosphere of rumour, pose a severe threat to the credibility of patient groups. Many are now trying to erect firewalls against inappropriate influence by renegotiating their relationship with the industry.

An unequal relationship

By law, pharmaceutical companies are not permitted to communicate with patients directly.

Europa Donna put on this breast cancer exhibition during its campaign to get policy passed by the European Parliament. Getting the right facts across to the right people at the right time can't be done on the cheap

Patient groups have been accused of acting as 'stooges' for the pharmaceutical industry

Building a relationship with a patient group gives them an avenue for getting information to patients about their products and research results, and can be helpful in recruiting to clinical trials. It gives them a chance to get feedback about how patients perceive their products and to identify potential gaps in the market. Support from patients can be very helpful in getting a new drug approved or onto the reimbursement list. A good relationship with patient groups also does wonders for the corporate image, and can be particularly valuable during a public relations crisis.

The relationship works both ways. Patients have an interest in the effectiveness, safety, side-effects and cost of drugs, and want to know about clinical trials they may be eligible for. Patient groups want to influence research and development and keep up to date with research results.

The industry and patient groups both benefit from a constructive relationship. The problem is that the relationship is unequal: pharmaceutical companies have money, scientific knowledge and expertise in marketing and public relations. Patient groups do not. When patient groups accept money from the industry, questions are asked about inappropriate influence. Is the group driven by the interests of patients or the agenda of sponsors?

Some patient groups refuse money on principle. They are, however, in a small minority. A survey of 45 groups who attended the first conference of the European Cancer Patient

A number of patient groups are now taking steps to ensure they don't get tarred with the same brush

Coalition in Milan last June elicited 22 responses, covering nine countries: Belgium, Germany, Italy, Netherlands, Poland, Romania, Spain, Sweden and the UK. Results showed that 19 of the 22 (86%) receive industry funding on occasion. Two refuse money on principle. One is forbidden to accept industry sponsorship by its funding body, a national cancer charity.

Few of the 19 who accept industry sponsorship use this money to cover core running costs. The exceptions are in Poland and Romania, where there is little tradition of state or charitable funding for voluntary groups, and what there is, says Simona Ene of the Romanian Association of Cancer Patients, is not made available to cancer patient groups because of the appallingly negative attitude towards cancer in that country.

Sponsorship from four or five different companies is common. One group reported support from 20 different companies; none reported funding from a sole sponsor. The money tends to finance particular projects: public awareness campaigns, information leaflets, newsletters, organising conferences and travel costs.

The proportion of income derived from industry varied from marginal to well over 50%. It tended to be lower among groups with a focus on supporting and informing patients, and higher among groups geared heavily to promoting public awareness and advocacy, and among European umbrella groups, where travel and translation costs can be heavy.

The majority of groups have some form of policy on sponsorship, but it is rarely written down, almost never publicly available, and usually amounts to a vague commitment not to take funding from companies with a poor ethical reputation or accept funding with strings. Sponsors are often acknowledged on the back of publications or on a group's website, but very few patient groups have a policy on declaring sources of funding.

A recent survey of its affiliates by Europa Donna Italy revealed that just under one-third of the 67 groups that responded received sponsorship from the pharmaceutical industry, but only two had a policy document on transparency.

Few groups are aware of laws or regulations governing sponsorship. Deutsche Leukaemie- und Lymphom-Hilfe say they were obliged to sign a statement of good intent in order to accept sponsorship from the pharmaceutical industry without jeopardising grants from Germany's health insurance companies.

The overall picture shows that, in general, pharmaceutical companies choose what activities they wish to sponsor, but details of the size of the sponsorship, what it is used for, and what they can expect in return are rarely disclosed in full.

Renegotiating terms

Lack of clarity and transparency does not mean that inappropriate relationships are being deliberately concealed. In fact, cancer patient groups tend to be strongly driven by patients' priorities, as one might expect of groups run largely by people who know what it means to have cancer.

But bad practice does exist, and a number of cancer patient groups are now taking steps to ensure they don't get tarred with the same brush. Central to this has been a move to define relations with industry sponsors in quasi-legal detail. The European Cancer Patient Coalition defines four types of funding – 'sustaining partnerships' (unrestricted grants of at least 20,000 euros as one among a group of sponsors), project funding, sponsorship, and smaller unrestricted grants. It spells out what input sponsors get into a project, the nature of acknowledge-

ments and what sponsors can expect in return. As well as guiding principles, it sets guidelines for commercial companies governing the use companies can make of ECPC's name and logo and the avenue of communication between the companies and ECPC, down to the terms on which ECPC will deal with companies' public relations agencies.

The ECPC policy borrowed ideas from similar documents drawn up by other patient groups such as the European Organisation for Patients with Rare Diseases (EURORDIS). Other patient groups, including Europa Donna (the European Breast Cancer Coalition) and the Global Lung Cancer Coalition, have used the ECPC guidelines to beef up their own policies. New European groups will be able to draw on these policies. In this way a new and more transparent relationship with the industry is being forged.

The concept of a 'sustaining partnership' or 'founding partner' is becoming increasingly popular as a way of receiving funding that can be spent entirely as the patient group sees fit. The traditional model of sponsorship for particular projects opens patient groups to allegations that their activities are skewed towards issues of commercial interest. Conferences, newsletters, information leaflets and websites are of interest to the industry because they all help spread awareness about the latest treatments. Campaigns to cut waiting lists for radiotherapy or to ensure that cancer surgeons treat a minimum number of patients per year are of less interest, and therefore less likely to receive funding. Using the sustaining partnership model enables patient groups to follow their own agenda.

Efforts are also being made to avoid being tied too closely to a single sponsor – something for which the Global Lung Cancer Coalition was criticised in the Australian press. The Coalition had been set up from a meeting organised by AstraZeneca, who also initially provided the secretariat. Jesme Baird, a founding member, said "We all knew it didn't look transparent from the outside to have just one company supporting us, and we felt the coalition should be more independent." The secretariat has now been taken over by the UK Roy Castle Lung Foundation, and more companies have come on board to finance activities through a sustaining partnership agreement. Baird argues, however, that the Coalition has been a huge boost for lung cancer patient groups, who struggle with a unique set of difficult problems. She insists that without AstraZeneca taking the initiative, it could never have got off the ground.

International umbrella groups in the process of formation, such as Myeloma Euronet, are learning from that experience. Even if they are set up with the support of one particular pharmaceutical company, there does appear to be a recognition that it is important to bring in other industry partners at a very early stage.

It takes two...

Renegotiating a relationship does, of course, require the agreement of the other side. This may be less difficult than expected, as the industry is aware of the need to polish its image. Relations with an increasingly confident and critically minded set of patient groups will also suffer if pharmaceutical companies are perceived to be acting in a cynical and manipulative manner.

Six years ago, the European Federation of Pharmaceutical Industries (EFPIA) drew up a Memorandum of Understanding with Europe-wide patient groups. In 2003, the Swedish Federation drew up its own ethical guidelines, which rule out, for example, core funding. The British Federation is currently reviewing its

Some companies are beginning to move away from a purely commercial relationship

Do you know your risk? Mamazone used shock tactics to get Germany talking about breast cancer

Code of Practice. The current version makes no explicit reference to relations with patient groups, but the Federation expects the revised version at the end of this year to cover this.

This change of approach seems to be reflected among big companies, at least at the European level.

Catherine Steele, International Head of Public Policy at Roche, says the company is moving away from a purely commercial relationship with patient groups to a more carefully structured and transparent ongoing relationship. Steele confirms an industry-wide change away from funding individual projects towards a greater use of unrestricted grants. Companies are increasingly playing a sustaining role, she says, because many of the international organisations would otherwise not survive.

AstraZeneca recently hammered out a formal policy on its approach to patient groups. Head of public affairs in oncology, Lynn Grant, says that this aims to achieve "long-term and mutually beneficial relationships … based on transparency and trust."

Smaller patient organisations may, however, be less able to negotiate unrestricted grants. For example, Romanian pharmaceutical companies recently rejected an approach from the Romanian Cancer Society for a 10,000 euro partnership agreement.

Is it enough?

Some argue that any cooperation between patient groups and the industry necessarily shifts the patient group towards the industry agenda. Anita Hardon of the University of Amsterdam says that the influence is inevitable and often subconscious. Writing in a Dutch newspaper, she says that patient groups tend to focus on medical rather than non-medical treatments, and tend to take the same line as drug companies.

Jenny Hirst of the UK Insulin-Dependent Diabetes Trust, giving evidence to the UK parliamentary enquiry, put it this way: "You cannot criticise the pharmaceutical industry and specific drug companies and take their money at the same time."

Ulla Ohlms, of the German breast cancer advocacy group Mamazone, rejects what she calls 'fundamentalist' arguments, and says that Mamazone does criticise companies it receives money from, for instance, about the excessive price of drugs. Jesme Baird, of the UK Roy Castle Lung Cancer Foundation, says that if

Mamazone criticises companies it receives money from, for instance, about the price of drugs

The EC needs the existence of umbrella groups to consult with, but gives them no financial support

you are professional and remember that you are there for patients, you have no compunction about criticising a company when appropriate. Both point out that patients have pressing reasons for wanting access to certain drugs, and should not be denied the right to speak out just because a sponsoring company could benefit.

Consumer watchdog Andrew Herxheimer, writing in the *British Medical Journal* (31 May 2003), argues that the key is to be transparent, take money from a variety of sponsors, and keep the industry contribution down to no more than 20% of total income.

Few argue against transparency or multiple sources, although there can be practical difficulties with declaring all small donations, while 'rare disease' organisations can find it difficult to attract multiple sponsors.

There is less consensus, however, over the 20% limit.

For the bigger national and European patient advocacy groups, which make the patient voice felt in the policy arena, the 20% formula doesn't seem to work in the absence of other funding. These groups equip cancer patients with the information and skills they need to argue in a variety of arenas, for more and more appropriate research and better prevention, screening, treatment and palliative care. To do this, they need to be up to date with research, knowledgeable about healthcare systems and policy, familiar with political processes and able to communicate effectively with their members, policy makers, healthcare professionals and the public. None of that comes cheap, while working at a European level entails travel and translation costs.

Some, such as the Swedish breast cancer group BRO and the NFK (Dutch Federation of Cancer Patient Associations) receive substantial unrestricted national funding from the state or national charities. But they are the exceptions.

German health insurance funds are meant to set aside half a euro per member to fund patient groups. However, Ohlms of Mamazone believes that the grants are out of step with the needs of today's cancer patient groups; Mamazone has never been able to access such support or even to verify whether health insurance funds really distribute what they should. UK groups can apply for potentially generous grants for specific activities from the Department of Health. But like commercial companies, governments only fund projects that match their own priorities.

The European Commission's consultation processes require the existence of European umbrella groups, but the EC gives them no financial support. Most umbrella groups are therefore dependent on the industry.

It appears that the European Medicines Agency (EMEA), which is currently developing its own policy document on relations with patient groups, recognises this reality. EMEA is expected to reject setting an upper limit to the proportion of income from pharmaceutical funding, focusing instead on issues of transparency, disclosure of direct and indirect funding, and on ensuring no single company has a dominant position.

There has been talk in the UK about establishing an independent body to 'kite mark' patient organisations on the basis of transparency, sources of funding, membership size, internal democracy and so on. However, the National Institute for Clinical Excellence (NICE), which draws up guidelines for treatment and takes decisions over which drugs should be reimbursed, has not seen such a bureaucracy to be necessary.

Marcia Kelson, Director of the NICE Patient Involvement Unit, says the industry cannot unduly influence NICE through patient representatives, "because whatever submission they make we will use to go and

Some patient groups resent people who are free from cancer staking out the moral high-ground

look at the evidence to see whether it supports what they said." She says that NICE is perfectly capable of differentiating between a methodologically sound randomised survey undertaken by an established patient group and a letter-writing campaign put together by an organisation established to lobby for a particular drug or treatment.

Honest debate

This issue is not new, but the stakes have been raised as decision-making structures at a national and European level open themselves to greater patient involvement, and patient groups become more assertive and effective. Between the highly pragmatic attitude of NICE and the arguments of the 'fundamentalists' are many shades of opinion and ideas on how to move forward, and new policies and contract-based funding models are being developed even as the issue is debated by politicians and discussed in the media. However, industry influence is not the only issue here.

Some patient groups resent what they see as people who are free from cancer staking out the moral high-ground with little regard for the adverse impact they may have on patients. Nor do the accusations over 'tainted money' seem to value the thousands of hours of voluntary labour provided by the members of these groups, which in most cases are worth many times the value of industry sponsorship. Many groups rely on volunteers to provide counselling, support and information to other patients, staff a phoneline, run a website or newsletter, write and produce information leaflets, travel to conferences and sit on committees.

Nor are critics of these groups always motivated entirely by ethics. Ohlms talks of the time Germany's health minister Ulla Schmidt attacked Mamazone for "sticking together with industry" after the advocacy group had voiced criticisms of the Government's forthcoming disease management programme. Ohlms feels this comment was a cheap alternative to responding to the issues.

If this debate is to be honest and constructive, then those who contribute need to be respectful of the people with cancer and what they have at stake. For every alleged 'stooge' organisation there are a hundred groups kept going by patients of tremendous bravery, selflessness and dedication.

They have brought hope and comfort to hundreds of thousands of patients, and have been a driving force towards patient-centred research and care.

All groups need funding, from Europa Donna, which successfully lobbied for a European Parliament policy on quality breast cancer care, to cash-strapped patient groups in Romania who are trying to secure chemotherapy pumps, drugs and safe blood products within a system that considers cancer an automatic death sentence.

Simply attacking an important source of funding in the name of ethics and independence will not help them. Supporting them in their attempts to secure their independence through negotiating new terms with industry and finding alternative sources of unrestricted funding will.

For every 'stooge' organisation there are a hundred groups led by patients of tremendous dedication

Cancer nurses
partners in care

Peter McIntyre

Cancer nursing is changing across Europe. Nurses are studying to higher levels, taking greater responsibility and making more autonomous clinical decisions. One important result is that they are better able to help cancer patients make sense of what is happening and learn to become partners in their own care.

Cancer nursing developed as a specialty in the 1970s. At the Royal Marsden Hospital in London – one of three specialist cancer hospitals in the UK – Robert Tiffany encouraged other cancer nurses to study up to Masters level and extend their role in prevention, early detection, care, and even in an intensive care setting. He was inspirational in starting the International Society of Nurses in Cancer Care (ISNCC) and in 1984 was a founding member of the European Oncology Nurses Society (EONS).

The Royal Marsden is still a European leader in cancer nursing. In 2000, Shelley Dolan became nurse consultant in cancer critical care here, the first nurse in the UK to be made a consultant. Her consultancy involves her in work across the UK and internationally. Dolan chairs the Royal College of Nursing Cancer Care Forum, is on the board of the ISNCC and is an active member of EONS.

She says that almost all cancer patients want more control of their lives. "If you are to be master of your own destiny and you have a chronic illness, most people would like to be well informed and a partner in decision-making. To control pain and manage their condition at home, it is important that they understand what is going on."

Intensive care

The critical care unit at the Royal Marsden is an intensive care unit for cancer patients, who are likely to be on a ventilator and need cardiac monitoring or kidney support after complex major surgery. Patients are also admitted for treatment of a life-threatening renal failure, respiratory failure, cardiac arrest or major bleed, as a result of their cancer or treatment. The mean stay is three to four days, but 20% stay longer – up to 44 days.

Despite the relatively short length of stay, it is important, says Dolan, for nurses to get to know their patients. "This is an acute blip in a chronic illness and they could have many more blips, so it is really important that they have the best experience possible, or they are going to be scared if they have to face surgery again in three years' time. When I employ a critical care nurse,

Shelley Dolan, nurse consultant in critical care at London's Royal Marsden Hospital. She was the first nurse in the UK to be made a consultant

I am looking for technical expertise, knowledge and experience, but I am also looking for someone who can give a lot of love to the patients. They have a very hard diagnosis to deal with and the family has a very hard diagnosis to deal with. Suddenly you are in this environment where there are bells and buttons and machines all around you; it is very scary for you and your family. It is very important to me that we do everything you would expect a supportive care nurse to do. Even when the patient is sedated and on a breathing machine we talk to them as though they can hear every word that we are saying."

Contact continues after discharge, through a critical care 'cool off' service to help people with cancer cope with their psychological and emotional reaction. "As soon as they are discharged from the unit to the ward, one of my critical care outreach nurses makes sure that they are recovering and goes through any worries that they have.

"They come back to my clinic at three months, six months and a year. I do a physical examination but also let them tell their story of their critical illness, to make sense of what can be a very disorientating time, where night and day get confused. People may think they have been in a film. It can be very florid. They sometimes develop what we call 'critical care psychosis' where they think that everyone is trying to kill them and that the doctors are Russian spies. We help them to make sense of it, as though their brain needs a bit of help to put these images and flashbacks into the right place."

This story telling is now part of a research project at the Royal Marsden, and Dolan says that many patients express immense relief when they find they are not the only ones to have been deeply affected.

Cancer nurses administer chemotherapy, manage symptoms, and must understand the progression of the disease and possible side-effects of treatment. Dolan sees one of the key roles of her nurses as providing a point of reference and education for their colleagues. "Haematological conditions, such as leukaemia, lymphoma and myeloma, are quite complex diseases, and most intensive care nurses only see a

small number of those patients a year. These nurses will not necessarily understand about the complex chemotherapy, bone transplant and why patients are so sick."

The specialist knowledge of nurses is increasingly recognised across Europe as an important factor in patient outcomes. Experience has shown that knowledge and training of nursing staff is essential for optimal cancer care. The Wisecare+ project in a number of centres, including the Royal Marsden, showed the benefits of using new technology to help patients keep in touch with nursing expertise even after they leave hospital.

Pain reduction

One of the key roles of nurses is to minimise pain for patients. People with cancer often fear pain as much as any other aspect of the disease and in 90% of cases this can be effectively controlled.

At the Royal Marsden patients are asked before an operation where on a scale of 1–10 they would want their pain control following treatment. Dolan says that most cancer patients are stoical and realistic and, rather than asking for a 0, ask for pain to be kept to no more than a 3 or a 4.

"If you have had major surgery you will not do well afterwards unless you have good pain control. You have got to be able to breathe well so you can come off the ventilator, you have got to be able to cough and you have got to be able to walk, to avoid things like thrombosis. Patients in pain won't cough and won't do their physio properly and won't be able to walk about and will get all the complications that can arise. Pain is not just damage to a nerve. It is about sadness and anxiety. It is linked to our memory. If surgery was excruciating last time, that is what you think it will be again and it will be harder for us to achieve pain control."

Another important skill is to be able to understand patients' concerns and to explain clearly what is happening and about choice.

Dolan says that this means learning to listen, as people may express their real thoughts in casual throw-away remarks. "When people give us cues we need to hear them. When you are giving an injection if someone says 'I'm not sure if I am going to get through this' it is much easier to say: 'Of course you are. Don't worry' and rush off to do something else. But that would not be listening to the person; and would not meet the standards we want. It is much harder to expose yourself to their pain, their sadness and their fear."

Dolan rejects the idea that you have to choose between technical competence and a good bedside manner. "You do not want a science textbook on the ward who cannot relate to the humanity of the person who has cancer. On the other hand you do not want someone who is warm and fuzzy but does not understand the drugs and how they work. Healthcare is complex and you are delivering drugs that are very toxic. To expect nurses to look after people without a good education to the level of a degree is a big mistake. Some of the best bedside nurses are very highly qualified." And she points out: "All doctors have medical degrees, including the caring GPs and palliative care physicians who have a really good bedside manner.

"I hope we get to a stage where we all realise that total care of the patient is the aim and it is actually much more rewarding to work like that," says Dolan.

In the UK, nurses are able to prescribe if they have done an extended pharmacology course, but this has not yet arrived in the complex world of oncology. Dolan believes it will come sooner rather than later. "Our critical care outreach service is very much nurse led. Nurses carry out a physical examination of the patient, assess them and need to prescribe care. What

"I would like nurses to be rewarded financially and in career advancement and to feel supported"

Shelley Dolan with student nurse, Lai Man Chan. Dolan argues that nurses who care for patients with complex diseases like cancer, and are expected to deliver toxic drugs, need to be educated to degree level

they have to do at the moment is to run to find a junior doctor who will prescribe what they want. That is obviously not ideal. We want to bring fast appropriate access to care for patients."

Teamwork

In specialist centres like the Royal Marsden, the hierarchy between professions has largely disappeared. Dolan says: "We work as part of a multidisciplinary team, and surgeons, anaesthetists, intensivists and physicians hugely appreciate the work of the nurses and the nurses hugely appreciate them. They are all very keen that we work together to improve the system."

She feels nurses in general deserve greater appreciation and recognition. "I would want to see nurses across the world having access to study leave and study resource so that more nurses could undertake postgraduate degrees. I would like them to be rewarded financially and in career advancement. I want nurses to feel loved and supported in their work. It is a tough job and junior doctors and nurses do not go home and switch off. They go home and they worry. They need to know that they are appreciated. That hard-nosed culture – come in, get the work done and go home again – I don't believe that that applies in healthcare."

If the nurses have changed, so have the patients, 80% of whom are cared for at home. Dolan recalls: "When I first came into nursing many patients would just say 'that's fine' whatever you say. Until very recently cancer was not talked about to patients – so people had a 'lump' or a 'bump' or some 'abnormal tissue'. Now many patients come in having studied the Internet. They want to know about options and what is happening.

"If someone is going to have a disease for the rest of their life, they had better know about it, because they are going to have to manage their finances, their family and everything else and we are not going to be there. Health is not just about the medicines you take. It is about the food you eat. It is about whether you stop smoking and if you take exercise. The most fundamental area of healthcare is about getting people more healthy. It does have to be a partnership."

Portrait of palliative medicine
as a young art

Raphaël Brenner

This is an excellent reference book for anyone involved in palliative care. It covers every aspect of the specialty, and is accessible to medical professionals and lay readers alike.

Since it first appeared 12 years ago, the *Oxford textbook of palliative medicine* has become the gold standard text in its field. But palliative medicine is a fast-developing subject, and much has happened in the intervening period, as we can see in this new paperback edition.

From a mere handful of palliative care services, there are now over 8000 worldwide. The subject is being taught in many more medical schools and has acquired specialty status in several countries including the UK and Romania.

However, there is still a long way to go. Even in the affluent West, "for every person who receives good palliative care there must be hundreds or even thousands who need it and have no access to it," write the authors.

They argue that the skills of palliative medicine depend first and foremost on attitudes, and they insist that a change in attitude is needed on the part of doctors "towards their patients, their needs and their care."

On every page, the book reaffirms the interrelation between the three groups involved in palliative care – patients, their families and health-care providers – the importance of pluridisciplinarity and the need for respect. "If people know they are respected as part of the human family (and here developing countries have much to teach us), the ending of life can be a final fulfilment of all that has gone before," notes Cicely Saunders, while a patient tells us "Loneliness is not so much a matter of being alone as of not belonging."

Oxford textbook of palliative medicine
3rd edition
Edited by Derek Doyle, Geoffrey Hanks
Nathan Cherny and Kenneth Calman
Oxford University Press, 2005, 1269 pp
£59.95 (paperback)

This latest edition contains so many changes and innovations that it should almost be seen as a new book. Its 21 sections, written by authoritative, international contributors, deal with every aspect of palliative medicine: from the cultural, spiritual aspects of palliative medicine to symptom management of cancer, from paediatric palliative medicine to complex ethical and emotional issues.

Marking the importance with which the subject is regarded by the authors, the section on education and training has been almost entirely rewritten, and includes new chapters on the role of humanities in palliative medicine and on new technologies such as Internet learning.

Also new are chapters on complementary medicines (aromatherapy) and alternative medicine, and on the contribution to palliative medicine of allied health professions (music therapy, psychology, etc.).

While cancer remains at the centre of palliative medicine, much space is also devoted to non-malignant diseases and to new approaches to neurological disorders.

Finally, an excellent section on palliative medicine in the home reminds us that there are still a fortunate few who die in their own homes (24% in the UK, 56% in Italy).

While this is clearly a medical textbook, non-physicians will also find in it a wealth of knowledge. It is stimulating, thoughtful, and has an open-minded global approach. My only regret is that the layout could have been less cramped.

Neuroonkologie
Edited by Uwe Schlegel
Michael Weller and Manfred Westphal
Georg Thieme, 2005, 492 pp
euro 99.95

The editors and 24 co-authors of the second revised edition of this textbook of clinical neuro-oncology have managed a pedagogical tour-de-force.
They have made the complex issues involved in their discipline accessible to physicians, general practitioners and oncologists alike, without compromising on either depth or detail – the bibliography contains more than 2000 references.
Their approach is practice-oriented and up-to-date – they use the WHO 2000 classification for description of tumours.
The comprehensive content is complemented by a clear and well-designed layout. Plenty of pictures, diagrams and tables, together with the use of two-tone printing and boxes, combine to make it very user-friendly.
The authors also deal with various aspects of interdisciplinarity in neuro-oncology, including the treatment of tumour-induced pain and psychosocial rehabilitation.
This book is part of the Thieme Reference Series in neurology.

Supportive care of children with cancer:
Current therapy and guidelines from the Children's Oncology Group
Edited by Arnold J. Altman
The Johns Hopkins University Press, 2004, 434 pp, $33.95

Written by the Children's Oncology Group, the world's largest cooperative study group for children's cancer, this third edition of *Supportive Care of Children with Cancer* is a highly useful, ready-reference handbook for nurses, medical staff and oncologists involved in paediatric oncology care. It can be consulted for quick reviews at a patient's bedside and is fully up-to-date. Today, three out of four children with cancer can be cured. But the downside is that children with cancer have to undergo increasingly intensive treatment regimens. This book details the supportive care measures needed to sustain children through therapeutic ordeals and enable them to achieve the best possible quality of life. A significant contribution to the improved outcome for children with cancer is the recognition of the infectious, metabolic and haemorrhagic complications that can arise in disease and treatment interventions. The book covers these complications in depth and describes new approaches to pain management. It also includes a new chapter on burnout among paediatric oncology staff.

Sam à l'hôpital
Marianne Almira
Gallimard jeunesse/Giboulées
2005, 48 pp
euro 12.50

"To find oneself from one day to the next in hospital because one has just been diagnosed with leukaemia is like undergoing punishment, except that no one has done anything wrong," writes Marianne Almira at the beginning of her book. Better than any textbook on psycho-oncology or supportive care written by scholarly physicians, *Sam* is a unique, first-hand testimony of a 13-year-old girl who was diagnosed with leukaemia.
To pass the time during the year she spent in hospital, Marianne drew her dog Sam as the cancer patient subjected to treatment by nurses and doctors. The result is an amazing strip-cartoon book illustrated and written with wit, sensitivity and intelligence.
It is a kind of hospital diary that is at the same time moving, funny (as when the physician prescribes the patient a blood test in an incomprehensible technical language), deeply instructive and full of hope. Through *Sam*, Marianne reveals to readers the unintended inhumanity of some medical staff.
Her book is a graphic portrayal of the feelings and needs of cancer patients. A must for everyone involved in oncology.